1. INTRODUCTION

1.1. HEALTH EXPENSE

The world is worried about the **Global Burden of Disease** (GBD), which is one of the main causes of governments' burden of state budget.

The latest data from the Organization of Economic Cooperation and Development **(OECD) countries** (with the exception of Hungary and the Netherlands because no data was available), tell us that health spending was on average 9,1% of Gross Domestic Product (GDP) and that the average expenditure on health *per capita* using the purchasing power parities (PPP) was US (United States) $2.839,9.
In the **US**, total health expenditure, in 2004, was $1.792 billion (15,3% of GDP), reaching a *per capita* expenditure of $6.156,9 (PNS, 2004-2010).
According to a recent study covering the nineteen **European countries** that belong to OECD, the total health expenditure *per year* in Europe, calculated using PPP was €844 800 million, or €1.872,1 *per capita* (Araújo, Barata, Barroso, Cortes, Damasceno, Parreira, Espírito-Santo, Teixeira, & Pereira, 2009), which is a lot less than the health expenditure in the US.

Considering data from 2004, the total expenditure on health in **Portugal** was 9,5% of GDP (13.591,4 billion €) and *per capita* expenditure was € 1.303,29 (Ferlay, Autier, Boniol, Heanue, Colombet & Boyle, 2007), lower than the average European countries that belong to OCDE, and much lower than the amount spent in the US.
Public spending on health in the country reassembled to 73,2% of total health expenditure (9.948,9 billion €), being 58,2% (7.911,7 billion €) funded by the National Health Service (NHS), and the remainder funded through public subsystems and through tax deductions from expenditure on private health. The direct expenditure of households totaled 20,6% of health total expenditure. Nevertheless, with the recent measures applied to contain spending in the country, there has been a reduction of the

rate of growth of public expenditure in 2003 and 2004, respectively of 6,6% and 6,0%. (Ferlay *et al*., 2007).

But is health becoming cheaper to the Portuguese? The answer is no! In fact, in 2004, private expenditure on health increased 7,9% (Ferlay *et al*., 2007). Secondly, preliminary data from the study of Jonsson & Wilking (2007), suggest that the total health expenditure in 2005 was 9,7% of GDP (14,4499 billion €) and that *per capita* expenditure was € 1.369,74, 72% of which was related to public spending. This means that the health expense is still growing and that Portuguese are directly assuming a bigger part of the expense amount, since the private health expense percentage continuous to grow too. This results are supported by the data presented in the Spring Report of the Portuguese Observatory of Health Systems (2009) that revels that in 2006, the total health expenditure was 10,2% of GDP, 70,5% of which were public funded (and 29,5% private funded).
Something has to be done to stop this growing tendency escalade. Economic measures have to be applied has soon as possible.

Health economics is a branch of economics concerned with issues related to scarcity in the allocation of health resources and health care. On the other hand, the **economic evaluation of medicines** is one of the most important branches of heath economics, since drugs are responsible for a huge burden on health (responsible for an expense of 2,2% of GDP, representing 23,9% of total health expenditure, in 2002 in Portugal (PNS 2004-2010)) and so, they are a major concern for governments, which strongly try to regulate the sector.
A major group of potential users of economic evaluation is **health care decision-makers** (Drummond, 2003).

1.2. THE BURDEN OF BREAST CANCER

Despite every effort made in prevention, early detection and treatment, **cancer remains a public health problem**.

Information based on the Portuguese National Plan for Oncologic Disease Prevention and Control (PNPCDO, 2007/2010) and from Araújo *et al.* (2009), tells us that **cancer is the second main cause of death in Portugal** (the first being cardiovascular disease). However, for population between 45 and 74 years, cancer is the leading cause of death, being responsible for more than 30% of deaths at those ages.

Data from INE (2007) showed that in Portugal, the mortality tax due to cancer has stabilized in around 10 deaths per 10^3 or in 2,1% per 1000 inhabitants. In 2005 were registered 107.839 deaths in resident population, being 23.232 (21,5%), cancer associated (Araújo *et al*., 2009).

Also note that, according to data from the *Oncology Hospital Referral Network (RRHO*, 2002), in Portugal cancer represented about 23% of the total years of potential life lost (YPLL), while cardiovascular diseases contributed only to 14%. Projections for the year 2010 show that the YPLL associated with cancer will represent twice as many attributed to cardiovascular causes (Chart n.1).

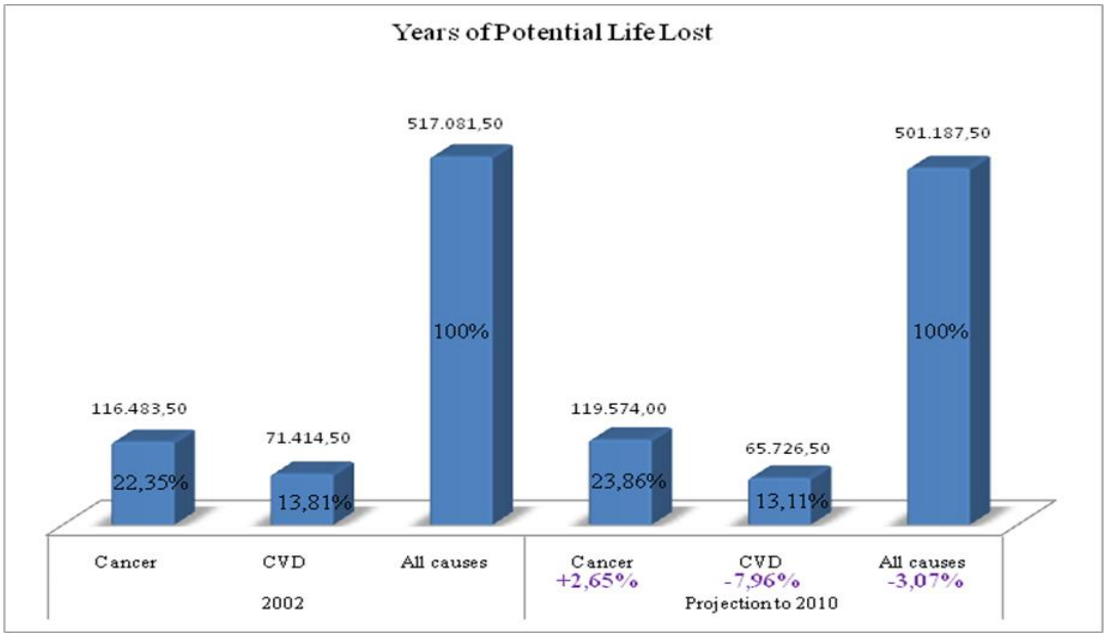

Chart n.1: Years of Potential Life Lost due to Cancer, CVD and All Causes in 2002 and Portuguese Projection to 2010.

Source: Addapted from the Heath National Plan 2004-2010.

Like it is shown in the previous picture, YPLL due to cancer are expected to increase 2,65% from 2002 to 2010, while YPLL due to cardiovascular diseases are expected to decrease around 8% and, due to all causes, to decrease 3%.

Considering the age range (Chart n.2), note that YPLL due to cancer will register a significant increase in the neonatal stage (25%), and a slightly increase after age 25, being more pronounced in the elderly (age range 65 and plus). However, this tendency is expected to be contradicted from young children with 1 year of age to the 25 age group. YPLL due to all causes are expected to be lower at all age ranges.

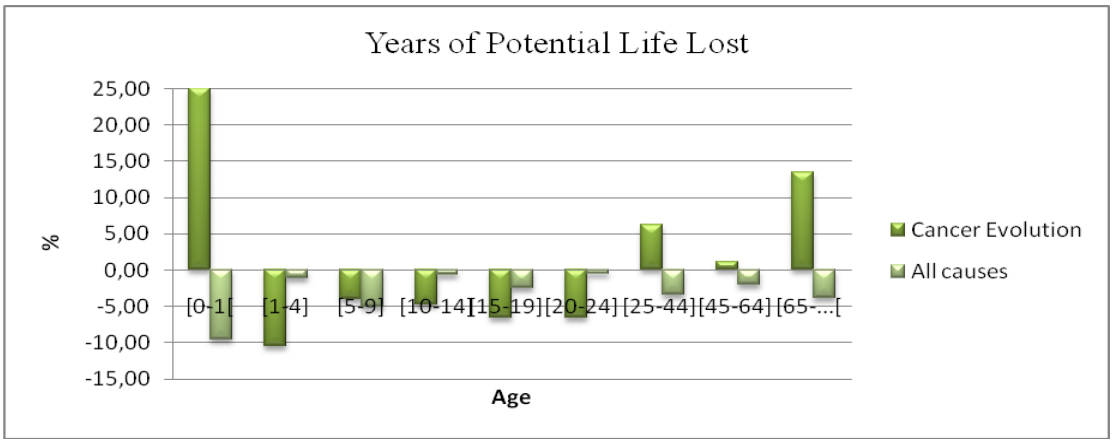

Chart n. 2: Evolution of Years of Potential Life Lost Due to Cancer and All Causes from 2002 to 2010, With Age Range.

Source: Adapted from Heath National Plan 2004-2010.

The *Portuguese National Plan for Prevention and Control of Oncologic Disease (PNPCDO,* 2007/2010) described a study were, in 2000, were attributed 1.122.000 deaths from cancer in 25 European Union (EU) member states, and were had been estimated that by 2015, this number will increase by nearly 11%, to 1.249.000 deaths.

In fact, **cancer has a highly associated mortality tax**, in addition to a **high incidence rate**. Most recent cancer incidence Portuguese National Data, belong to the National Oncologic Registration from the year 2001, when were diagnosed 33052 new global cancer cases (Incidence Rate of 328,3%ooo) and when around 55% of the diagnosed cancer were from male gender and 66% from ages 60 years-old and plus. Data from a European cancer incidence and mortality estimation study, from 2006, tells us that

Portuguese cancer incidence age standardized rate was 428:100.000 in men and 289:100.000 in woman (Araújo *et al*., 2009).

Approximately one million women are diagnosed with breast cancer each year worldwide, according to published data of different sources and general scientific publications (Radice & Redaelli, 2003).
Incidence and mortality rates vary widely in different countries: they are high in most industrialized countries (except Japan), intermediate in Eastern and Southern Europe, and low in Central and tropical South America, Africa and Asia (Radice and Redaelli, 2003). Breast cancer (BC) is the most common cancer found in women in Europe (180 000 patients per year), and it represents 20% of all malignancies. Rates in Western Europe range from 40–60 per 100 000 women. The lowest incidence is observed in some areas of Japan (approximately 12–15 per 100 000 women) and the highest incidence rate is observed among women living in Canada (British Columbia; approximately 80–90 per 100 000 women). Furthermore, scientific community assumes that one in eight women in the US (United States) will develop breast cancer during their lifetime and that the incidence rate will roughly double for every 10 years of life until menopause (Radice & Redaelli, 2003).

Comparing the cancer mortality indicators for Portugal with the best of EU countries, Portugal is expected to be able to reduce premature mortality by 38% in men and 10% in women. This percentage had been proposed to the decrease of breast cancer mortality in the country in the RRHO (2002), having the ***Health National Plan (PNS,* 2004-2010) established breast cancer as a priority** (Macedo, Andrade, Moital, Moreira, Pimentel, Barroso, Dinis, Afonso, & Bonfill, 2008). In 2002, in Portugal, **the most common types of cancer were breast cancer** (13.5%) and cancer of the colon and rectum (12.9%) (PNPCDO, 2007/2010). **Breast cancer remains the leading cause of cancer death in women**. Data from the Portuguese PNS (2004/2010) estimated the female mortality rate related to breast cancer, based on expectations of specific mortality rates by age, **showing a high growth tendency with the increasing of age and a slight decrease tendency with time evolution (Chart n.3)**.

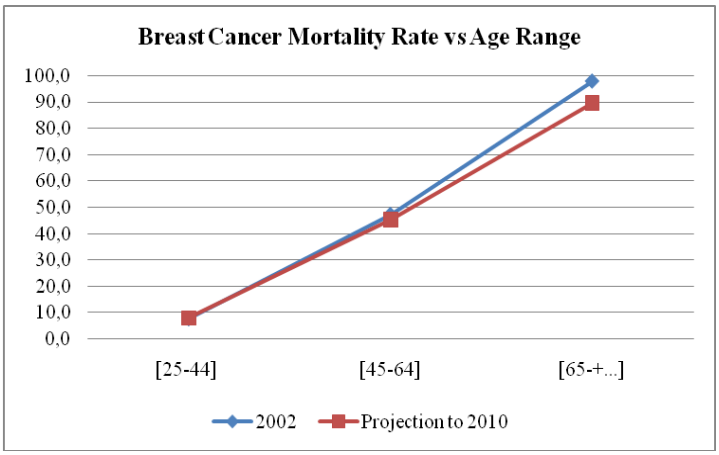

Chart n. 3: Evolution of breast cancer mortality rate with age and time.

Data Source: Adapted from PNS 2004-2010.

This decreasing tendency was supported by the study of Barros, Barros & Lunet (2007), on mortality evolution from breast cancer in Portugal, between 1955 and 2002. Results showed that there was a change in the variation of mortality tax in the early 90s, with a decrease of 2% per year between 1992 and 2002, with sharper declines in districts with higher rates of mortality, such as Lisbon. In women aged between 35 and 74 years, mortality from breast cancer increased by 1.55% per year (confidence interval (CI) 95%) from 1955 until 1992; and it ranged -2.02% / year (95% CI) between 1992 and 2002, which is a good indicator of the mortality rate associated with BC.

Besides the **high mortality rate associated**, BC also has **high morbidity**.

Although for most patients the disease is limited to the breast and nodes, for which surgery followed by systemic therapies are potentially curative, around 50% of patients diagnosed with early breast cancer will eventually progress to an advanced form of the disease and advanced breast cancer is not curable. While the treatment aim for early breast cancer is the cure, for advanced breast cancer is to slow down or stop tumor growth for some period of time, whilst retaining an adequate quality of life for the patient (Karnon & Jones, 2003).

It is well known that immigrants assume the incidence rate in the host country within one or two generations. This suggests that environmental or lifestyle factors

(reproductive history, diet, …) may be more important than genetic factors for the incidence of BC (Radice & Redaelli, 2003).

However, in many parts of Europe, including Portugal, the advances in prevention, early detection and treatment, which ultimately contribute to lower the rates of BC mortality, begin to be sufficient to mitigate the sharp increase in the number of deaths due to oncology of an aging population (chart n.3). Scientific evidence reported within the PNPCDO (2007/2010) show that **cancer screening programs in breast cancer led to a reduction of mortality rates** of around 30%, meaning that these are important measures to follow. The Portuguese means or protocols to fight cancer are described in the *National Oncologic Plan (PNO)*, which includes all stages that accompany the disease, from prevention and screening to diagnosis and treatment, completing the rehabilitation and palliative care. The national policy of screening for cancer, under the Ministry of Health, focuses greatly on BC. The main widely promoted method of screening is self-examination of the breasts and armpits, an annual mammography from age 40 to 65 early in cases of family history and mammography every 2 years among women of 50 to 69 years (PNPCDO, 2007/2010).

In 2009, the breast cancer screening program geographical coverage included 74,5% of the Portuguese main land councils (figure 1). However it has been estimated that this coverage will rise to 84,5% in 2010, achieving the global Portuguese territory in 2011 (Information Bulletin n.4, 2009).

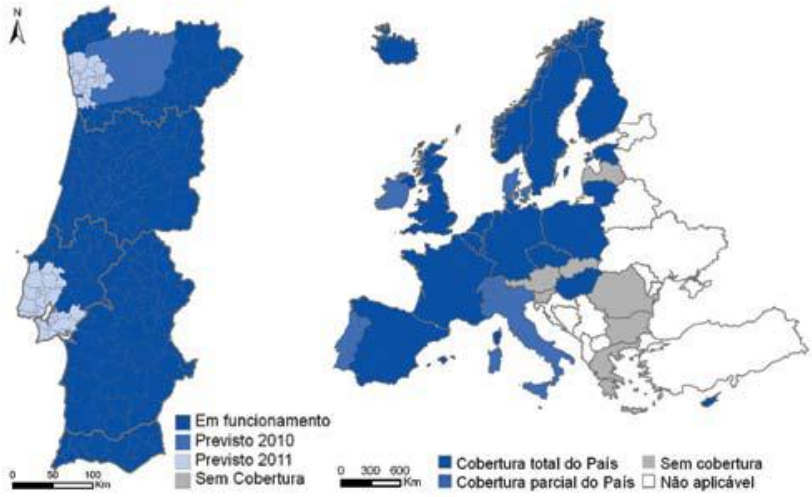

Figure 1: Breast Cancer screening program geographical coverage. Darker territory signals complete coverage.

Source: Made by the GIP/ACS and supported by the data from the LPCC, CNDO and ARS, 2009.

The cost of care for patients with BC is substantial. As the projected incidence rates of breast cancer are likely to increase, the associated costs will also rise.

	Cancer direct cost (million €)	**Cancer direct cost *per capita***	**Cancer cost in relative % to health costs**	**Total health cost (million €)**	**Population 2004**
Netherlands	1502	92	4,1	36 643	16 275 000
Hungary	495	49	5	9 897	10 107 000
Poland	1 138	30	5	22 758	38 180 000
Czech Republic	514	50	5	10 287	10 211 000
France	7458	124	5,3	140 714	60 200 000
Germany	12 108	147	6,6	183 455	82 491 000
Sweden	1 316	146	7	18 802	8 994 000
United Kingdom	10 823	182	10,6	102 100	59 554 000
Portugal	565,03*	53,33	3,91	14 500**	10 595 600***
USA	62 321	212	4,7	1 325 988	293 655 000

Table n. 1: Cost of Cancer Treatment. Data from OCDE (2004).

Source: Araújo *et al.* (2009)

* Data for 2006 relating to GDH's hospitalization, chemotherapy, radiotherapy and drugs.

** Data for 2005; *** Data for 2007.

In the previous table we can observe the results obtained from several published studies based on OECD data for the cost of cancer treatment, using PPPs adjusted price of 2004. In US (2004), 4,7% of total medical costs were from cancer and expense in direct medical costs of cancer was 62,3 billion dollars. To highlight the growing trend in cancer investment in the US, it had been estimated that the expenditure allocated to direct cancer costs in 2006 ascended the 78,2 billion dollars (Reeder & Gordon, 2006).

In Portugal there are few data available to determine the actual cost of cancer. In their study Araújo *et al.* (2009) tried to minimize this fact, calculating the cost of cancer in the country. With this goal in mind, they used the number of episodes of hospitalization (as referenced by their *Homogeneous Diagnosis Groups (GDHs)*) and the number of medical consultations to determine the cost of cancer. It was considered the cost of drugs (outside hospitals). From the previous table we can see that in Portugal the direct cost of cancer treatment reached 565 million €, which represents 3.91% of total health

expenditure and about 53 € *per capita*. The *per capita* expense for Portugal is much lower than what we find in other EU countries, being only comparable to the newly integrated countries in the EU such as the Czech Republic, Hungary and Poland.

There are two major areas of cancer treatment costs: those associated with hospitalizations and associated with outpatient treatment. According to data on the cost of cancer, we can estimate that nearly 60% of the costs fall on hospitalizations, and 37% are assigned to outpatient treatment (Jonsson and Wilking, 2007).

Given the available data, we can observe the distribution of the cost of cancer treatment in the country (table n.2).

Oncology GDH Price (2006) *	313 792 774 €
Chemotherapy Cost (admitted patient) (2006) *	17 365 170 €
Radiotherapy Cost (2006)	75 034 009 €
Day Hospital Chemotherapy Price (2006) *	125 882 086 €
Medical Consultations **	29 460 463 €
Oncology Drugs Cost – Pharmacy Shop (2006)	3 500 000 €
Total	565 034 503 €
Total Heath Cost Relative %	3.91 %

Table n. 2 - Cost of Cancer Treatment in Portugal

Sources: Data from ACSS, 2006, IMS Health, 2006; NHS Hospital Statistics Movement 2005; Return National Report, 2006; Ordinance No. 110A/2007.

* Spending on drugs is included in these GDHs

** Cost of consultations taken from the Cost Accounting Hospitals NHS, 2006: € 123.74 for oncology and € 51.93 for radiotherapy.

This table represents the sum of expenditure with oncologic GDHs, spending on Chemotherapy and Radiotherapy, and spending on cancer drugs outside the hospital (medicines bought in pharmacies) as well as medical expenses, in 2006.

When total costs of medicines by therapeutic area are calculated, it appears that drugs for cancer represent approximately 5.6% of total expenditure with medicines in 2006 (*IP Multimedia Subsystem for Heath (IMS*-Health) data for 2006). Considering the total cost of cancer, we can say that drugs for cancer account for 2% of total expenditure of cancer treatment.

The *Portuguese National Authority of Medicines and Health Products (INFARMED)* report of drug consumption in the Portuguese hospitals from February of 2009, tells us that **oncology is the activity area that represents the greater costs to the country**, with a relative weight of 25,2% of total hospital costs. The major impact on expense was found to be attributable to antineoplasic and immunomodulator therapy, medicines specifically used to treat cancer.

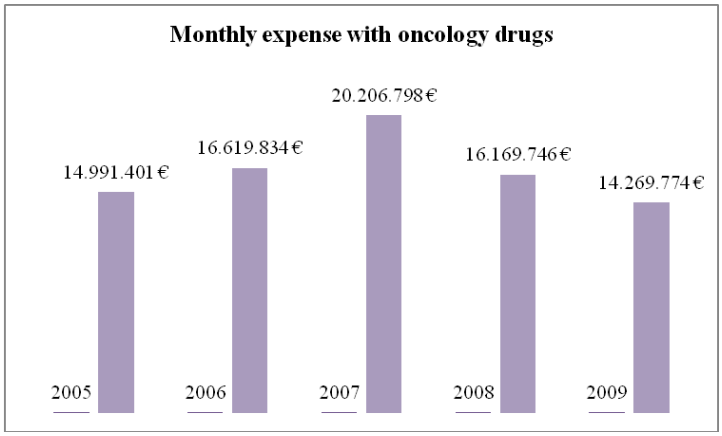

Chart n. 4: Monthly expense with oncology drugs in Portuguese hospital units.

These consumption data refer to the products covered by the National Code of Hospital Drugs (CHNM) that include drugs for human use with Market Introduction Authorization (MIA), Authorization for Special Use (AUE) and Authorization for Exceptional Use (AEX). Note that all medicinal products with CHNM provided by hospitals, regardless of the nature of funding, had been included.

Similarly, in Europe, in 2004, it was estimated that total expenditure on cancer drugs accounted for about 5% of total expenditure in medicines (Jonsson and Wilking, 2007). However, it should be noted that the *per capita* expenditure on medicines for cancer in Portugal is lower than that observed in the EU. The experts found that 26% of total spending on drugs for cancer treatment has been placed on medications for palliative care or support. Furthermore, if we compare the proportion spent on medicines in relation to the total cost of the disease, we found that although oncologic drugs represent an important part of the cost of cancer, their weight does not exceed 34% of total costs of the disease.

Given the burden of cancer in Portugal, the impact of direct medical costs and the expenditure allocated to cancer is significantly lower than the burden of cancer, it seems

reasonable to suggest that in Portugal, cancer appears to be insufficiently funded (Araujo *et al*., 2009). Although this should not be the only criterion to determine the volume of spending in a given therapeutic area, the gap identified in these authors study is large enough to merit the attention of decision makers.

Portugal showed a growing tendency of the expense with this type of drugs from 2005 to 2007, followed by a significant descent. However, we can't forget that trastuzumab is the more expensive active substance and docetaxel the fourth, both of them currently used in BC treatment.

The increased number of cases and the relative lack of effectiveness and safety associated with BC treatment led to the development of a multitude of treatments. Apart from therapies that already exist, patients may benefit from new associations or be involved in clinical trials of drugs with innovative mechanisms of action. The multiplicity options and practices make it extremely difficult to their assessment (Macedo *et al*., 2008), but efforts have been made and note the decreased monthly expense tendency registered from 2007 to 2009.

Moreover, the innovation in the field of oncology has brought great clinical advances but also problems in management efficiency. In a sensitive area is often difficult to decide based on the efficient choice. In fact, restrictions of healthcare budgets and the importance of quality of life in terminally ill patients have led to the thrust that new drug adoption in oncology must lie in establishing improved efficacy and tolerability of novel agents, which means that the collection of empirical cost-effectiveness data tends to be neglected. However, this information may be derived using decision-analysis models that make use of available evidence and expert opinion (Brown, Lipscomb & Snyder, 2001), like proposed in this study, that we believe will contribute to further decrease the cancer treatment expense.

In summary, all of the screening policies, added to treatment policy and new expensive treatment options (that even with small clinical benefits have become accepted treatments), an aging population tendency and the growing number of age related

pathologies (like BC), as well as investment in new clinical technologies, resources and medical progress, may translate a **gradual increase in the burden of BC in Portugal** and a consequent increase of the average health care expenditure, requiring the allocation of the available resources as efficiently as possible (Busse, 2001; Dedes, Matter-Walstra, Schwenkglenks, Pestalozzi, Fink, Brauchli, & Szucs, 2009). The decision analysis models are of extreme importance for this efficiency, contributing to decrease the cancer treatment expense, ultimate goal of this study.

1.3. THE STUDY RELEVANCE

Trying to fill some gaps within breast cancer therapy policy making (namely related to transparency of the criteria used for pharmacologic therapy selection for clinical use, hospital acceptance and reimbursement), and considering the data presented above, we can understand that *breast cancer is one of the most expensive pathologies*, which represents a huge burden to every country, that needs great attention and focus by decision-makers, responsible for prevention and treatment policies.

In addition, an *increased emphasis on evidence-based medicine* and justification for the use of healthcare interventions on the basis of economics as well as clinical factors has lead to a broader evaluation of new therapies (Brown, Lipscomb & Snyder, 2001). In fact, one of the aims of the Portuguese PNS (2004-2010) is centralizing the data relevant for the evaluation of health gains, both in the preventive or the objectification of medication effectiveness. One the other hand, the PNPCDO (2007/2010) "encourage scientific research in view of its contribution to improving quality of care promotion of clinical trials that explore issues related to therapeutic strategy, involving the main centers of cancer treatment in Portugal". This means that *every research is this field is welcome to the country*. This idea was supported by the study of Araújo *et al.* (2009), where it has been considered that in the present context, where spending on drugs continues to increase and resources available to finance new therapies are limited, there is a need to develop a study in the Portuguese context about the cost of cancer treatment, and specifically the cost of drugs used to treat the disease. This study is

crucial for informed decision making as regards the allocation of funds from the health budget to the area of oncology.

This is the result of an increasing recognition that *decisions relating to the allocation of resources in fixed-budget healthcare systems are of extreme importance to cost-containment*, and that on the other hand, decision-makers should be informed of the associated treatment costs as well as the relative effectiveness of the alternative interventions. In a high prevalence treatment area such as BC, aggregate treatment costs will rise quickly even if a treatment at the individual level is perceived to be inexpensive (Karnon & Jones, 2003).

Therefore, *decision-makers have been persuaded to increase their attention on the evaluation of economic analysis* of the impact of different therapeutical interventions in early stage and metastatic breast cancer, supporting clinical, hospital´s drug formulary, and reimbursement decision making.

Note that *economic evaluation offer potential advantages for the busy health care decision makers*, providing a substitute for undertaking an independent (and potential time consuming) literature research.

On the other hand, *decision analysis modeling is a useful tool* in situations where data are disparate and time constraints and financial restrictions preclude the prospective collection of cost-effectiveness data (Brown, Lipscomb & Snyder, 2001; Shi & Lyons-Weiler, 2007), which applies to cancer therapy. The publication of principles of good practice for decision analytical modeling in healthcare evaluations by a task force from the *International Society for Pharmacoeconomic and Outcomes Research (ISPOR)* provides evidence of the vital role of modeling *for decision makers in the public and private sectors* (Weinstein, O´Brien, Hornberger, Jackson, Johannesson, McCabe, & Luce, 2003).

These are the **main reasons why we had chosen to dedicate this thesis to the development and implementation of a breast cancer therapy cost-utility analysis model**, able of helping decision makers to do their job in a transparent, credible and efficient way.

A considerable amount of health decisions take place daily at the point of the clinical encounter; especially in primary care an in hospital specialized oncology units. Since every decision has an opportunity cost, ignoring economic information in clinical decision-making may have a broad impact on health care efficiency (Lessard, 2010). Note that **Oncologists** don't have a specific tool to help them to decide if an alternative pharmacologic therapy for breast cancer is cost-effective and therefore more adequate for each specific patient, being simultaneously efficient in terms of costs for the oncology unit of the hospital and for the *quality adjusted life years (QALY)* of the patient. This tool would therefore help clinicians to separate risks and benefits, compare the added value of different therapeutic interventions in a given clinical context and present more balanced information about treatment options to patients (Epstein, Leung, Mak & Cheung 2006).

Likewise, in the current formulary decision process, each drug product is evaluated by members with expertise in medicine (physicians, pharmacists, nurses, and administration agents) that belong to the **hospital´s committee of pharmacy and therapeutics**. The committee evaluates information from the drug manufacturer and other independent sources, and makes an initial assessment with respect to clinical aspects of alternative therapies and generic interchangeability, than considers the administrative and economic implications of accepting the product for the patient, the program, and healthcare professionals' practice (Nash, 1994). The committee doesn't have a tool to help them to decide if an alternative pharmacologic therapy for BC is cost-effective relative to the drugs most commonly used and included in the hospital formulary, for each specific cancer situation. In the study of Walkom, Robertson, Newby & Pillary (2006), despite the relatively low reported usage of pharmacoeconomic data in decision making, most respondents considered this information to be "somewhat" or "very" important. Similarly results were reported in the study of Odedina, Sullivan, Nash & Clemmons (2002).

The CHEUAL prototype is based on specific variables, rules, and criteria used to evaluate drug products for formulary inclusion. As previous studies had demonstrated, computer-assisted decision support systems (as we intend to transform CHEAUL BC model) can be readily applied to pharmacy practice (Nash, 1994).

Portuguese legal rules to evaluation of medicines into hospital´s formulary introduction can be appreciated in **Appendix n. 1**.

On the other hand, economic evaluations have become an important and much used tool in aiding decision makers deciding on reimbursement or implementation of new health-care technologies (Stolk, 2004). The **decision makers of drug's reimbursement** have been criticized by many industry pharmacists and economists, which argue that the criteria adopted to decision making are ambiguous (Wilder & Dupont, 2008). These authors suggest that evidence of therapeutic value, besides costs and budget impact analysis, plays a significant role in the drug reimbursement decision making process.

Stahl (2008) says that simulation modeling methods to evaluate the cost effectiveness of different clinical and policy strategies have been estimated to cost < 5% of the total time and budget of a given project and to have a very rapid and large return on investment, on the order of 1000%.

Moreover, until the present moment, we haven´t knowledge of the existence of any capable of being adapted to a computer program and used worldwide model for the evaluation of the impact of different therapeutic interventions in early stage and metastatic breast cancer, supporting clinical, hospital's drug formulary, and reimbursement decision making in a simple and credible way.

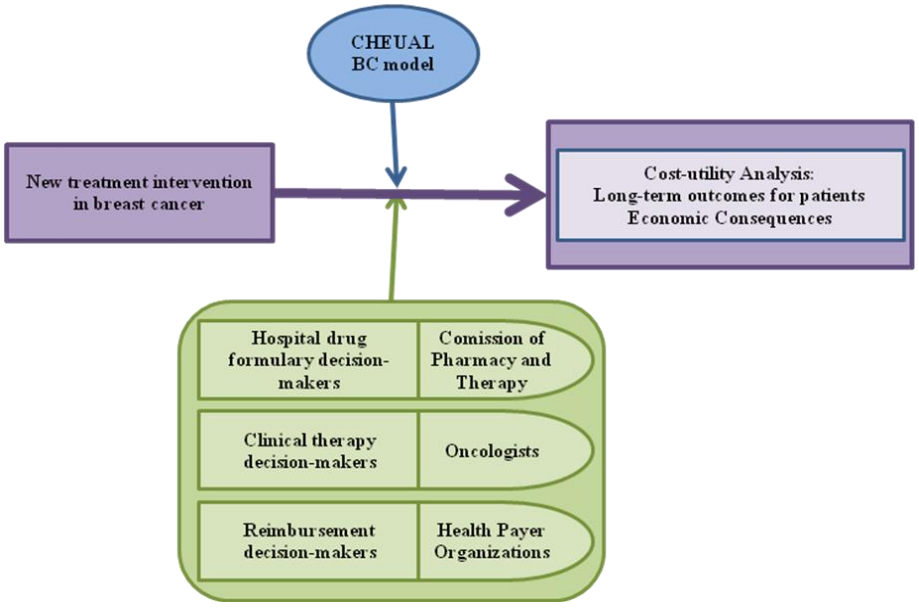

Figure n. 2: Scheme that translates the research idea.

Source: Own construct.

The CHEUAL breast cancer model *(from the Center of Health Economics of the Universidade Autonoma de Lisboa)* is an open cohort simulation model that allows the comparison of BC pharmacologic therapy current practice with the introduction of a new product.

Previously explored health economic models of the modern era must be able to support decision-making. However, to fulfill this role, models need to be accepted by relevant providers of care target groups, especially by medical experts' and healthcare payers. Therefore models should be transparent, with users having access to full description of how they work and the data upon which they are based. In addition, the complex nature of advanced models of chronic illness means that clear descriptions are required to assess the credibility of the assumptions used to create the model. This is what we will try to accomplish within this study.

Note that, as convertible to a software, this model is likely to be integrated in the Network of Referenced Integrated Oncology (PREC), described in the PNPCDO (2007/2010) as a priority that should be establish as a system that integrates different types of institutions to provide a specialized care in oncology in the near future, facilitating communication between the institutions responsible for cancer care and therefore creating conditions for the standardization of procedures, improving the accessibility and efficiency.

In the current context, in which expenditure on medicines continues to increase and the resources available to finance new therapies are limited, it is crucial to make decisions based on the true value of cancer treatments in terms of health benefits, costs and savings for the *National Health Service (NHS)* (Araújo *et al*., 2009).

1.4. OBJECTIVES

A study of economic evaluation must have clearly defined objectives. This implies to ask a question which will be addressed through the empirical work. Thus, any study is conditioned by how that question is asked (Silva, Pinto, Sampaio, Pereira, Drummond & Trindade, 1998; Stahl, 2008).

The **main global objective of this research** is to develop and validate a model that would allow physicians, pharmacists and reimbursement decision makers do an economic evaluation of pharmacologic treatment interventions in early stage and metastatic breast cancer, helping them to do their job in a transparent, credible and efficient way.

Trying to answer this question, others more specifics seem to follow. These research questions can be identified as **specific objectives**, stated as:

1. Which data/variables are important to include in BC pharmacologic therapy economic evaluation?
2. Which type of economic evaluation is more adequate to this kind of study?
3. Which kind of model should be used to simulate the progress of breast cancer complications and thought, disease progression?
4. What is breast cancer incidence/prevalence in the country?
5. How can consequences be estimated?
6. What is the cost of BC therapy, considering ambulatory chemo/hormonal and immunotherapy?
7. How can this model be validated to further use?
8. How will be used?

1.5. METHODOLOGY

To achieve our goal, the research will be divided in five parts:

- First, the theoretical development of the CHEUAL breast cancer model, which implicates the collection of secondary data like scientific papers and legal documents, with the help of the B-On database.;
- Secondly, the model construct, integrating all the input and output variables within the data processor;
- The third part will assess the validation of the model;
- The fourth, will present an example of the application of the model, simulating the cost-utility analysis of a new drug therapy (paclitaxel in association with bevacizumab) versus the therapy most currently used in the treatment of patients with metastatic breast cancer, in Portugal, through a clinical/oncologist/physician perspective.

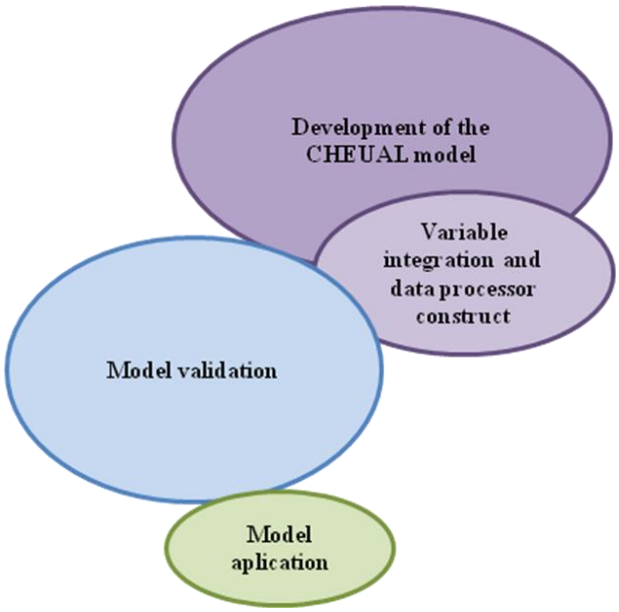

Figure n. 3: Scheme of the parts that compose the research strategy.

Source: Own Construct.

2. THEORETICAL BACKGROUND

2.1. HEALTH ECONOMIC EVALUATION FOR COST-CONTAINMENT POLICY

Health care decision makers are increasingly considering economic information when choosing between competing therapies and prevention strategies for acute and chronic disease. Because such information must be timely to have impact, economic analyses are now commonly conducted alongside prospective controlled clinical trials (Rovira, 2008).

Although standards for conducting high quality clinical trials have been recognized for decades, the notion that economic analyses could (and should) be conducted alongside clinical trials has only recently been recognized as important (Briggs & Levy, 2006).

As is discussed below, *cost-effectiveness or cost utility analyses (CEAs or CUAs, respectively)* are not necessarily easy to be performed at the same time as clinical trials, because the purposes of the studies are often distinct and occasionally in conflict. Nevertheless, several forces have contributed to the proliferation of joint clinical/economic trials. In the US, perhaps the most compelling reason has been the perception that decision makers need information about the potential economic impact of new therapies as they diffuse into the market (Ramsey, McIntosh & Sullivan, 2001). In particular, pharmaceutical manufacturers have been willing to expend resources to establish that their expensive new products are still economically attractive because they reduce the rate of (and therefore cost of managing) morbid endpoints related to disease. Other reasons include the strong internal validity of randomized controlled trials and the relative efficiency of conducting joint clinical/economic studies. Because of these advantages, the Panel on Cost-Effectiveness in Medicine noted that "the most common primary study design used in CEA is one in which economic and additional health outcomes are added onto a randomized controlled clinical trial" (Ramsey, McIntosh & Sullivan, 2001).

Despite the interest and apparent popularity of joint clinical/economic trials, the literature on design of such trials is limited. In 1984, Drummond & Stoddart first

outlined many of the pertinent issues researchers face when conducting economic analyses alongside clinical trials. Seven years later, Adams, McCall, Gray, Orza & Chalmers (1992) reviewed the prevalence and completeness of economic analyses alongside clinical trials, finding deficiencies in both the quantity and quality of such studies.

Nevertheless, the Task Force on Cost-Effectiveness in Medicine, convened in 1993, provided no explicit recommendations for designing joint clinical/economic trials. Perhaps in response to the relative lack of guidance, specialty societies have developed their own guidelines for including economic endpoints alongside cancer clinical trials (Ramsey, McIntosh & Sullivan, 2001). Portugal was not an exception. In 1998, Silva *et al.* developed the *Methodological Orientations for Economic Evaluation of Medicines in Portugal*, which is still the main guideline in the country in our days (**Appendix n.2**).

Strategies for cost containment in the pharmaceutical sector include measures whose aim is to influence the market, from the supply side and from the demand. While the supply-side strategies focus on the pharmaceutical industry (essentially over price control), demand-side strategies operate on patients or on health care providers (doctors and pharmacists, in their capacity as patients agents), with the objective of minimizing the problem of induced demand, making the provision of medicines more cost-effective. The use of economic evaluation studies (mainly in France, Sweden and UK), is considered a strategy of cost containment in the pharmaceutical sector on the demand side, operating on physicians and pharmacists (Mossialos and Barros, 1998).

Hurst, in the assessment of the impact of health economics on health policy in England, during the period 1972–97, Buxton (2006) suggests that health economics may arguably had, at least as significant, an effect on the process and language of policy making as it had on the content of particular policies. This author considers that economic evaluation plays a major role in the Appraisal Committee´s decision making, in the UK. In his work he reports a growing acceptance of the value of the *Incremental Cost-Effectiveness Ratio (ICER)* from committee members, in helping them to manage the complexity of decisions. Consistently, Chabot and Rocchi (2010) reveal in their study that Canadian oncology decision-makers have reimbursed cancer drugs at incremental cost-effectiveness ratios higher than those considered acceptable in other therapeutic areas.

In Portugal, every new drug proposed for reimbursement is obligated to present to INFARMED an economic evaluation analysis proving the incremental benefits (ICER) for the new treatment option. Portuguese legal rules for drug reimbursement approval can be found in **Appendix n.3.**

2.2. THE COST-UTILITY ANALYSIS OF MEDICINES AS A MEASURE OF ECONOMIC EVALUATION

When we study economic evaluation, there are some concepts that me must keep in mind.

Efficacy is the measure of the beneficial effect of a technology / strategy evaluated under ideal conditions (in a controlled environment in the context of a clinical trial); and *Effectiveness* is the extent of the beneficial effect of a technology / strategy evaluated in terms of current clinical practice. This is why studies of economic evaluation data are primarily interested in the effectiveness when the national reality is reflected (Briggs & Levy, 2006).

At the launch of a new product, only efficacy data exist and so, it is inevitable that the studies carried out at this stage have to extrapolate the effectiveness of therapy from the estimated efficacy in clinical trials. Normally, for this purpose there are used modeling techniques (Silva *et al.*, 1998).

The measures used to assess the *therapeutic effect / consequences* are:

- Measures related to the disease, usually physical measures (reduction of blood pressure values);
- Measures related to the patient (reduction of motor disability, number of life years gained);
- Quality of life measures; and
- Monetary units. (Silva *et al.*, 1998)

When the consequences are evaluated in terms of measures related to the disease or to the patient, the studies to be undertaken are the *cost minimization analysis (CMA)* or cost-effectiveness analysis (CEA); quality of life measures may be undertaken in cost-

utility analysis studies (CUA); and at last, if we are considering monetary units we must undertake *cost-benefit analysis (CBA)*.

The **analysis technique** chosen should be adequate to the problem under study and this adjustment must be justified.

If is demonstrated that the consequences associated with all alternatives investigated are identical (rare), it is assumed to hold a **CMA**, where, due to the impact of therapeutic equivalence, we should only consider the costs.

When the consequences associated with different alternatives are not identical, we can use a **CEA**. This technique responds to two types of question: what therapy can achieve a level of pre-set effectiveness at the lowest cost; and which therapy maximizes the cost-effectiveness at an overall pre-determined cost. We can use several measures of effectiveness, from clinical observations (such as the reduction in blood pressure) to the number of deaths avoided. The fundamental issue is that the measure of effectiveness has to be appropriate and common to the treatment under study.

If differentiation of the alternatives can only be made considering multiple consequences possibly not common to the alternatives, as it happens with cytostatic drugs used to treat BC, it should be adopted a CUA or a CBA (Silva *et al.*, 1998). These approaches allow the comparison of the results of studies that refer to different pathologies.

Health outcomes represent the ascribed benefits of an evaluated medical intervention. These outcomes can be ascertained during the observation period of the study or extrapolated from beyond the study period using mathematical or other estimation methods (Rovira, 2008).

Taxonomy of possible health outcome measures for **CEA** would include measures of averted morbidity, surrogate clinical markers, life extension, health related quality of life, disability-adjusted survival, and quality-adjusted survival. For example, researchers have used treatment-specific measures such as sight-years gained, symptom-free times,

cases of disease prevented, and change in likelihood of progression of disease in the denominator of the cost-effectiveness ratio. The problem with these measures is that they are treatment or disease specific (Ramsey, McIntoch & Sullivan, 2001). From a clinical perspective, measurement of treatment-specific effects is advantageous because they can be quantified more precisely with treatment-specific measures. From a resource allocation perspective, the health policy analyst would prefer to have a common and standard measure of health outcome that extends across different diseases and treatments. This facilitates the comparison of cost-effectiveness studies.

Unfortunately, no consensus exists on which of these outcome measures is most appropriate, although the US Panel on Cost-effectiveness in Medicine suggests using QALYs, because they link to welfare theory and fit within a resource allocation and social utility framework (Garber & Phelps, 1997). Quality-adjusted survival has been defined as the duration of an individual's life as modified by the changes in health and well-being experienced over the lifetime. The next figure depicts this concept as the area under the curve.

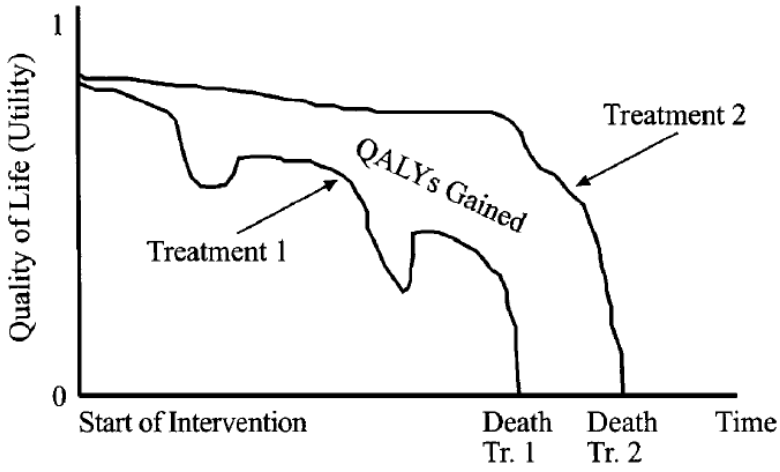

Chart n. 5: QALYs gained using a new therapy.
Source: Ramsey, McIntoch & Sullivan (2001).

In theory, aggregating individual-level QALY measures would give the cost-effectiveness analyst an approximation of the societal benefit of an intervention.

A practical approach to selecting an outcome measure would be to assure that all cost-effectiveness analyses employ the same outcome measure (QALY) so that standard

decision rules for resource allocation would apply (Ramsey, McIntoch & Sullivan, 2001). That is, health policy makers will set funding priorities for health care expenditures by selecting those with cost/QALY ratios less than a willingness-to-pay threshold previously defined (as we will discuss later).

The CUA can thought be seen as a form of CEA where the consequences are measured in terms of life years gained, weighted by the variation in quality of life, expressed as QALYs. The weighting factors should reflect the aggregation of individual preferences for the outcome of therapeutic intervention, and can be directly estimated from patients or from the general population, obtained from published data or estimated based on panels of experts. The output described provides an assessment of the extra costs and benefits of an intervention when compared with another treatment option (Brown, Lipscom & Snyder, 2001).

The CUA is sustained by the economic theory and is the technique of economic evaluation which has registered higher growth in the health field, and was therefore the analysis technique chosen to measure the economic evaluation of pharmacologic therapy used to treat BC, in this study. This means that will be considered the *total per-patient cost of using one (new) therapy* and *the total per-patient cost of the therapy most commonly used*, as well as the *QALY values for the base-case scenario* for both therapies (Brown, Lipscomb & Snyder, 2001), aiming to compare the additional total cost per patient of the new therapy for an additional amount of QALY, with the same costs and benefits for the therapy most commonly used.

Generally, the acceptability of the cost per QALY appears to be a dominant factor at the domains of the *National Institute for Health and Clinical Excellence (NICE)*, in the UK (Buxton, 2006).

The **CBA** differs from the other methods of economic evaluation, since it values both the costs and consequences in monetary terms. It is based on the economic theory of welfare and allows public investment comparisons with sectors other than healthcare. However, CBA studies raise very complex issues of measurement, such as contingent valuation. According to Silva *et al.* (1998), CUA is preferred to CBA.

2.3. MEASURING THE COST-UTILITY OF PHARMACOLOGIC THERAPY IN BREAST CANCER

Like shown before, BC is associated with substantial morbidity and mortality, and imposes an enormous burden on both individuals and health systems. There are multiple alternative approaches to the treatment of breast cancer but very few epidemiological studies or clinical trials are able to measure disease progression and the impact of interventions on costs, quality of life and health outcomes over a lifetime. When such information is not available (being very expensive and taking years to produce results), mathematical modeling may be used to make inferences about future economics, quality of life and health outcomes and to provide data to aid decision making (Stahl, 2008). Therefore, it is opportune to review some of the most significant literature published on the matter of our study.

2.3.1. LITERATURE EVOLUTION

The approach to perform CEAs and/or CUAs of medical technologies has become standardized in recent years, with principles and procedures for analysis and reporting results, which should be adhered to. Despite general agreement on principles for cost effectiveness studies, there are several concerns about performing CEAs/CUAs alongside with clinical trials. One important concern of performing cost effectiveness studies within a clinical trial is that the clinical care that occurs in the trial is not representative of care that occurs in real medical practice.

Ramsey, McIntosh & Sullivan (2001) described the key questions when considering whether to incorporate CEAs/CUAs alongside clinical trials.

1. Is the disease/condition highly prevalent in society?
2. Does the disease/condition have a substantial burden in terms of morbidity or premature mortality?
3. Is the control arm, a treatment that is commonly used in clinical practice?

4. Is the treatment likely to substantially affect endpoints that are meaningful to patients, particularly health-related quality of life or survival?
5. Are meaningful differences in the endpoints for question 4 likely to be detectable between therapy arms within the time constraints of the trial?
6. Is it financially feasible to collect endpoints that are identified in question 4?
7. Is there likely to be a large difference in up-front costs between treatment arms?
8. If yes to question 7, is there likelihood that significant downstream cost savings can be realized for the new intervention?

Reviewing all the articles found that were relevant to this study, we have analyzed in detail the most important for early and metastatic breast cancer treatment. However, if several versions existed for a given model (e.g. the same model in several countries or the same model based on different follow-up times of the underlying clinical trial) we excluded older versions of the same more recently published model, unless potentially important changes in design and methods were observed between the different versions, as done before by Annemans, Moeremans & Lamarque (2008). This involves two risks. First, the timing of the publication of the papers may relate more to the publication schedules of the journals or other factors than the relevance of the information. Second, it is a rather subjective judgment whether a change in design or methods is to be considered important. Regardless these facts, this approach avoid duplication, which was the main intention.

This process led to a final list of 15 articles. The main features are shown in tables 3 and 4. Different designs and treatment schedules were applied in these trials:

2.3.1.1. Early Breast Cancer

Table n. 3: Cost-effectiveness and cost-utility analyses comparing alternative pharmacologic therapies for early BC

Study	Comparators	Country (perspective; discount rate C/c)	Model type	Baseline results	Sensitivity analysis	Conclusions
Locker (2004)	ANA, TAM	US (health service; 3%/3%)	Markov, 25 years time horizon	US$29132/LY US$23740/ QALY	One way: ICER remains under US$50000 Probabilistic: upper 95% CI US$80000/QALY	ANA cost effective vs. TAM

Delea, Karnon, Thomas & Bargout (2005)	LET, TAM	US (health service; 3%/3%)	Markov, lifetime horizon	US$33430/LY US$32326/ QALY	One way: lower 95% Cl for effectiveness US$70000 Probabilistic: upper 95% CI US$74008/QALY	LET cost effective vs. TAM
Mansel (2004)	ANA, TAM	UK (health service; 6%/1.5%)	Markov, 25 years time horizon	£11747/LY £11506/ QALY	Probabilistic: upper 95% CI £22491	ANA cost effective vs. TAM
Karnon, Delea, Papo, Bargout, Thomas & Jonston (2005)	LET, TAM	UK (health service; 3,5%/3,5%)	Markov, lifetime horizon	£13643/ QALY	One way: ICER remains under £30000 Probabilistic: upper 95% CI £22344/QALY	LET cost effective vs. TAM
Annemans, Moeremans & Lamarque (2004)	ANA, TAM	France (health service; 3%/NS)	Markov, 20 years time horizon	€13525/LY €12722/LY	Results robust to relatively large variations in risk reduction and cost estimates	ANA cost effective vs. TAM
Dedes, Szucs, Imesch, Fedier, Fehr & Fink (2007)	TRA	Switzerland (health service; 3%/NS)	Markov, 15 years time horizon	€19 673/LYG	Probabilistic: upper 95% CI €50000/QALY	TRA cost effective vs. standard treatment
Millar & Millward (2007)	TRA	Australia (health service; 3%/3%)	Markov, 100 years time horizon	Aus$13 739/ YOLS Aus$22 793/ QALY	Results robust to substance cost and treatment duration variations.	TRA cost effective vs. standard treatment
Macedo, Monteiro, Andrade, Cirrincione, & Ray (2010)	TRA	Portugal (health service and society; 3%/3%)	Markov, 45 years time horizon	NHS perspective: € 10 067/LYG € 10 595/ QALY; Society perspective: € 7400/LYG €7789/QALY	Results robust to actualization tax variations.	TRA cost effective vs. standard treatment
Van Vlaenderen Canon, Cocquyt, Jerusalem, Machiels, Neven, Nechelput, Delabaye, Gyldmark, & Annemans (2009)	TRA	Belgium (health service; 3%/1,5%)	Markov, lifetime horizon	€ 10 315/ QALY € 11 036/LYG	800 Monte Carlo Simulations Probabilistic: lower 95% CI €40000/ QALY	TRA cost effective vs. standard treatment

Legend:
Discount rate C/c - discount rate of costs and consequences; NS- Not Stated; LY – Life year; QALY – Quality-adjusted life year; QAPFY – Quality adjusted progression-disease free year; YOLS – Years of Life Saved; LYG – Life years gained
LET – Letrozole; TAM – Tamoxifen; ANA – Anastrozole; EXE – Exemestane; TRA – Trastuzumab

We identified five alternative estimates of the cost-effectiveness of adjuvant *aromatase inhibitors (AIs)* versus tamoxifen in early BC, covering the perspectives of the US, UK, and French healthcare systems. Two of these analyses provided cost-effectiveness estimates of extended adjuvant letrozole versus placebo, after 5 years on tamoxifen, from a US and UK health service payer perspectives.

All of the evaluations used a decision-modeling framework to extrapolate the observed rates of relapse and adverse events in relevant clinical trials to an extended time horizon in order to estimate the lifetime costs and benefits associated with the alternative treatment options. All of the evaluations used a cohort Markov model to describe similar, although not identical, patient pathways. The letrozole models appeared to describe the most complex set of BC stages (Karnon *et al.* (2005) and Delea *et al.*(2005)), including separate contralateral primary tumors, and loco regional recurrence stages, as well as differentiating between three sites of metastases (soft tissue, bone, visceral). The Mansel (2004) model combined contralateral primary tumors and loco regional recurrence. Annemans, Moeremans & Lamarque (2004) appeared to exclude contra lateral primary tumors.

All models appeared to represent adverse events in some detail, with most models presenting a range of minor and major episodes. The exceptions were the letrozole models, which only represented major adverse events.

US costs estimated were slightly higher in the Locker (2004) version of the anastrozole model, although the differences were not large. Treatment costs were significantly lower in the UK than in the US model. It is noted that there is no explicit recognition of primary care costs in any of the papers, which may be of relevance, particularly from the UK perspective where more emphasis is placed on primary care.

On the other hand, none of the evaluations attempted an indirect comparison of the cost effectiveness of the alternative AIs. Such comparisons appear feasible given the similarity of the control groups in the relevant clinical trials (as in 5 years on tamoxifen in hormone receptor-positive postmenopausal women), although there are subtle differences in the patient groups (different proportions of node-positive patients) and in the range of reported outcomes (the definitions and types of treatment-related adverse events presented).

A direct comparison of letrozole with anastrozole may be expected to show that letrozole is slightly more cost-effective.

Whilst letrozole has been shown to be potentially cost-effective in both node-positive and negative patients as a sequential adjuvant therapy (after 5years on tamoxifen), the AIs have not been evaluated separately as initial adjuvant therapy for small, low-risk BC. Most of these cancers have very good prognosis and recurrences are rare even in the long term. Therefore, the greater efficacy of AIs compared with tamoxifen becomes relatively less important in this subgroup of BC, whereas the drug cost and the spectrum of adverse effects will gain greater importance. AIs have not been evaluated clinically in premenopausal women or in women with *estrogen receptor (ER)*-negative disease.

A final generic issue concerns the comparability of cost-effectiveness analyses that use alternative models. It would be useful to have a 'generic' model into which new trial data in a particular disease area could be inserted to facilitate indirect comparisons between alternative therapies in different countries.

Indirect comparisons are, in fact, danger, since patient populations differ between trials, having different modeling assumptions and errors associated. The CHEUAL BC, being worldwide adaptable, may contribute to minimize this gap.

The analysis techniques used to evaluate the following four trastuzumab articles, were also all based on modeling by Markov models. Markov models consider long-term consequences of both the prevention and progress of BC in patients with *human epidermal growth receptor 2 (HER-2)* positive breast cancer at an early stage to later stages of the disease, such as the emergence of new recurrence or metastasis of primary tumors. All contemplated studies compare the clinical benefits of trastuzumab as adjuvant therapy in relation to non-use of trastuzumab. Although there are differences in the model structure of the various studies, a comprehensive cost-effectiveness of trastuzumab as adjuvant and its effects in various stages of health, such as tumor remission, relapse, progression of metastatic cancer and death, are similar.

Transition probabilities were obtained from clinical studies, articles and data specific to each country in which the utility values were obtained from scientific literature, and costs obtained from national studies.

Most of the analyses were performed from the third-party payer perspective (NHS), which included direct medical costs (acquisition and administration of trastuzumab plus costs of hospitalization and outpatient). Macedo *et al.* (2010) study had also considered

the perspective of society and though, also included indirect costs, of productivity lost represented by the patient.

Analyses consider the long-term effects of trastuzumab as an adjuvant therapy in a time frame that varies between 15 years and the duration of a lifetime (100years).

The cost of HER-2 testing in patients receiving trastuzumab was seen in some tests and not others. Note that the inclusion of the test or not is debatable, since it is generally regarded as current clinical practice at the time of BC diagnosis. It is considered so that the costs associated with the test are identical in both cohorts.

On the other hand, adverse cardiac effects associated with treatment with trastuzumab in early BC may influence the cost-effectiveness of the drug. Compared to conventional treatment, the incremental costs associated with the use of trastuzumab may increase due to costs associated with monitoring and treatment of cardiac effects, while the incremental benefits can be reduced by reducing the average life expectancy or quality of life related health. Thus, the costs associated with monitoring and treatments of adverse effects associated with cardiotoxicity of trastuzumab were considered in some analysis. The studies of Dedes *et al.*, (2009) and Millar & Milward, (2007) assume that the adverse effects associated with trastuzumab cardiotoxicity are transient and that do not increase the mortality rate.

Sensitivity analysis was performed for different parameters that can affect the results of the models. Overall, the results remained generally robust in the fundamental assumptions of the model. However, in the study of Van Vlaenderen *et al*., (2009) the ICER in most of the simulations remained below the stipulated.

Remind that, in recent years, various economic assessment were studies conducted in several countries, making it likely that the use of trastuzumab as adjuvant therapy in the treatment of early stages of BC HER2-positive, is cost-effective from the perspectives of the third-party payer and of the society. Considering the selected studies, in general, the introduction of trastuzumab in the therapeutic treatment of early breast cancer HER-2+, every 3 weeks for 1 year, after chemotherapy, presents a general incremental cost per *life years gained (LYG)* or QALY. Data were obtained from various sources, as other studies or expert panels, and extrapolated of clinical trials for the general population. This may limit the applicability of study results, because although the model can be robust to the assumptions made, data from the consequences and costs may not

be applicable to other geographic regions, due to differences in health systems, current clinical practice or unit costs.

All studies were performed based on selected clinical trial data. The limitations of clinical trials can also limit the clarity and robustness of the corresponding economic analysis, since most of the results of clinical trials may differ from actual clinical practice. For example, clinical trials have strict inclusion criteria, excluding from the outset certain populations, which in current clinical practice, could receive treatment with trastuzumab.

In the HERA trial (reported in Dedes *et al.*, 2009 and Macedo *et al.*, 2010 studies) were not included patients with early breast cancer with an ejection fraction of left ventricle <55% after chemotherapy. Moreover, the summary of product characteristics approved by the *European Medicines Agency (EMEA*, 2010) for the EU, does not explicitly exclude patients with heart failure, but advises caution when using and monitoring of trastuzumab. The effect of long-term cardiotoxicity and its interference in the cost-effectiveness of trastuzumab are currently unknown. The low incidence of severe cardiotoxicity associated with use of trastuzumab in the HERA study and the apparent reversibility of cardiac symptoms, suggests that the cardiotoxicity will not have a significant influence on the cost-effectiveness of trastuzumab as adjuvant. Thereby still, it is important to clarify the incidence and consequences of cardiotoxicity.

2.3.1.2. Metastatic Breast Cancer

Table n. 4: Cost-effectiveness and cost-utility analyses comparing alternative pharmacologic therapies for metastatic BC.

Study	Comparators	Country (perspective; discount rate C/c)	Model type	Baseline results	Sensitivity analysis	Conclusions
Karnon and Jones (2003)	LET, TAM	UK (NHS; 6%/1,5%)	Markov, lifetime treatment pathways	£2342/LY	Probabilistic: upper 95% CI £10 134	LET cost effective vs. TAM
Karnon, Johnston, Jones & Glenndening (2003)	LET, TAM	UK (NHS; 6%/1,5%)	Life table model	£8514/QALY	Probabilistic: upper 95% CI £10 134	LET cost effective vs. TAM
Delea, Smith & Karnon (2002)	LET, TAM	US (NHS; 3%/3%)	Life table model	$US 7410/LY	Probabilistic: upper 95% CI £10 134	LET cost effective vs. TAM

Dranitsaris, Verma & Trudeau (2003)	LET, ANA, TAM	Canada (NHS; NS)	Decision tree (limited outcomes)	TAM to ANA $Can 19600/ QAPFY ANA to LET $Can 1850/ QAPFY	One Way: Results robust	LET and ANA more cost effective vs. TAM; LET more cost effective than ANA.
Dranitsaris, Cottrell, Spirovski & hopkins. (2009)	alb PAC, DOC, PAC	Canada (NHS; NS)	Meta-analysis of clinical trial and published literature	Alb PAC to PAC $Can 56800/ QALY DOC to PAC $Can 730600/ QALY	One Way: Results robust	Alb PAC more cost effective vs. PAC; DOC less cost effective than PAC.
Brown, Lipscomg & Snyder (2001)	DOC, PAC, Vin	UK (NHS; 6%/ 1,5%)	Markov Model 3years time model	DOC to PAC £1995/QALY DOC to VIN £14055/QALY	One Way: Results robust	DOC more cost effective vs. PAC; DOC more cost effective than VIN.
Legend: Discount rate C/c - discount rate of costs and consequences; NS- Not Stated; LY – Life year; QALY – Quality-adjusted life year; QAPFY – Quality adjusted progression-disease free year; NHS - National Health System HT – Hormonal therapy LET – Letrozole; TAM – Tamoxifen; ANA – Anastrozole; EXE – Exemestane; alb PAC – Albumin bound Paclitaxel; PAC – Paclitaxel; DOC – Docetaxel; Vin – Vinorelbine						

The first four articles reviewed evaluated AIs when used as first-line therapy in metastatic BC and were considered to be cost-effective versus tamoxifen, from the UK, US and Canadian health system perspectives. The comparative analysis of letrozole and anastrozole as first-line therapy is subject to some uncertainty as a result of the chosen time horizon, although letrozole was suggested to be the more cost-effective therapy option as first-line therapy. Three broad methods for the evaluation of AIs for advanced breast cancer were identified. The complete Markov lifetime modeling approach (Karnon & Jones, 2003) described detailed patient pathways from the start of second-line therapy to death, providing a comprehensive estimate of the costs and benefits of letrozole. The life table approach (Karnon *et al*., 2003 & Delea, Smith & Karnon, 2002) was more conservative (for first-line letrozole) in assuming completely equal prognoses for patients following either first or second-line therapy. This assumption reduces the cost-effectiveness estimates for letrozole, as it has been demonstrated that first-line tamoxifen patients have an increased transition directly to palliation. This approach, therefore, does not incorporate the potential survival benefits associated with letrozole of keeping patients on therapy. The respective cost-effectiveness estimates for the life table approach and the complete modeling approach are similar. Hence, the combined validity of these two approaches is good. The final AI approach (Dranitsari, Verma & Trudeau, 2003) used a decision tree to describe the short-term outcomes of patients with

respect to their response to first-line therapy. This approach provided a less complete representation than the other reviewed studies, because of the difficulty in describing the progression between alternative stages over time.

The two last articles evaluated mainly *paclitaxel (PAC)* vs. docetaxel, in the UK and Canada, from the NHS perspectives, and both have controversial results. While the study of Dranitsaris *et al.* (2009) approach is based on a meta-analysis of clinical trials, Brown, Lipscomb & Snyder (2001) model is based on a three years Markov Model. Note that PAC has high toxicity associated and is therefore advised to follow-up patients for almost six years after final substance administration (as discussed later), meaning that this last article time horizon model is not adequate to the study purpose. The other study, more recent, brings an innovative alternative therapy albumin bound paclitaxel molecule (alb PAC), that turns to be more cost-effective than PAC itself, which deserves future research.
Both studies, however, were considered robust after one way sensitivity analysis.

2.3.1.3. Summary of findings

Despite the limitations inherent in all economic evaluations, the studies selected were generally well conducted and seem to consider the appropriate parameters, according to the justification given by the authors. The analyses fulfill most or all of the basic criteria for economic evaluation studies of medications, including the use of appropriate comparators, data sources, refresh rates and sensitivity analysis, with reasonable variation of key parameters. The results of sensitivity analysis consistently showed that the results were robust with regard to changes in assumptions of the models.
Some of these data are still being explored and shall surely a significant impact on economic analysis.
We think however, that it was advised to do economic evaluations of all the main current used protocol drugs in order to additional resource cost containment of standard procedures. Note that the main economic evaluation studies found were related to new drugs that were trying to impose itself on the market (and Pharmaceutical Industry

funding). The high incidence of BC (increasingly detected at an early stage of the disease) and high direct and indirect costs associated with it reinforces this need.

2.3.2. PROPOSED MODEL – CHEUAL BC MODEL

Reviewed the most relevant studies in the field studied, we think we are now prepared to propose our cost-utility analysis model do aid BC decision-making. According to Buxton (2006) and Rovira (2008), the use of decision models makes the nature of the uncertainties in the evidence transparent.

The scientific paradigms reflected in this research is constructivism since, inspired by the CORE diabetes model (Palmer, Roze, Valentine, Minshall, Foos, Lurati, Lammert & Spinas, 2004[a]), we will try to develop a model adapted to the therapy of breast cancer, the CHEUAL BC model, exploring some gaps detected on the first model and adding variables that had been used within recent published articles of economic evaluation analysis in BC. We will respect the methodological orientations proposed from the INFARMED for the economical evaluation of medicine studies in Portugal, since 1998.

Like it is shown in the scheme bellow (figure n. 4), the CHEUAL BC Model consists of five input data groups that users can or must modify every time a new simulation is made. To process this data, the model has seven database processor groups that are critical for the results accomplished, these last, represented by four output data groups.

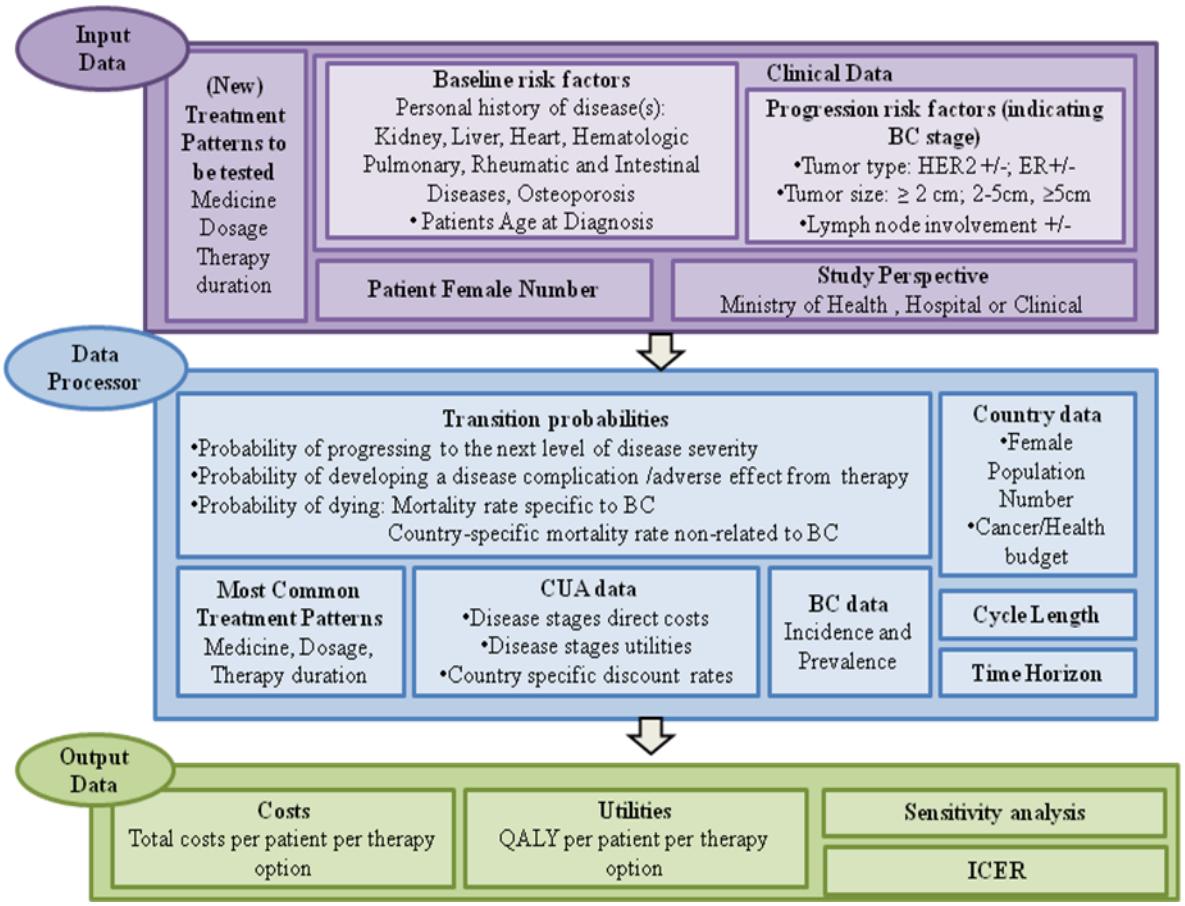

Figure n. 4: Scheme of the CHEUAL BC Model: inputs, data processor and outputs.

Source: Own construct.

In another perspective, we can also present the CHEUAL BC model represented by twenty hypotheses to test, expressed as follow:

H1: Study perspective positively influence the model output.

H2: Drug (new) treatment option costs positively influence the model output.

H3: The baseline risk factor personal history of disease, positively influence the model output.

H4: The baseline risk factor patients age at diagnosis, positively influence the model output.

H5: Progression risk factors, giving rise to disease stage (tumor type, size and lymphatic nodes affected), positively influence the model output.

H6: Currently used drug costs positively influence the model output.

H7: Global therapy costs positively influence model output.

H8: Global therapy QALY positively influence the model output.

H9: Country specific discount rate positively influence the model output.

H10: The time horizon of the study positively influence the model output.

H11: Treatment and/or disease complication positively influence the model output.

H12: Acute renal failure positively influence the model output.

H13: Acute hepatic failure positively influence the model output.

H14: Acute pulmonary disease positively influence the model output.

H15: Cardiovascular disease positively influence the model output.

H16: Osteoporosis positively influence the model output.

H17: Acute arthralgia positively influence the model output.

H18: Acute cytopenia positively influence the model output.

H19: Acute diarrhea positively influence the model output.

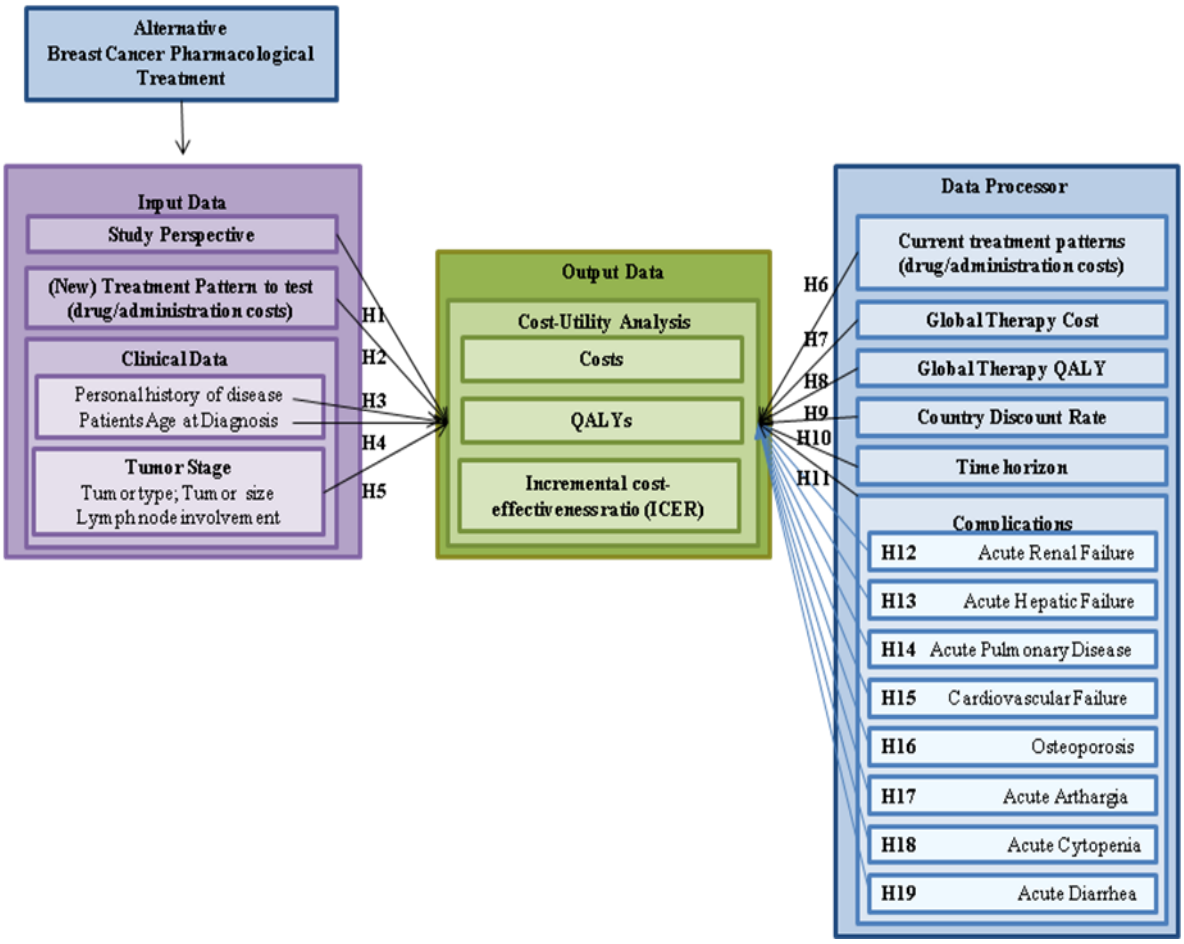

Figure n. 5: Scheme of the CHEUAL BC Model illustrating the hypothesis to test.

Source: Own Construct

As shown in this figure, the model proposes that study perspective, (new) treatment patterns to be tested, baseline risk factors (personal history of disease and patients age at diagnosis), disease progression risk factors representing BC stage (tumor type, tumor size and lymphatic nodes affected), current treatment patterns, global therapy cost and QALY, country specific discount rate, time horizon, as well as the eight disease / treatment complication sub-models of transition probabilities (acute renal failure, acute hepatic failure, acute pulmonary disease, cardiovascular disease, osteoporosis, acute arthralgia, acute cytopenia, and acute diarrhea), positively influence model simulation output.

2.3.2.1. INPUT DATA

Information stored in the input database forms the basis for the calculations required to run each simulation performed by the data processor.

As **input data**, the model incorporates patient number estimated to the new therapy (Palmer *et al*, 2004[a]), (new) treatment patterns to be tested (Brown, Lipscomb & Snyder, 2001; Dedes *et al*., 2009; Karnon & Jones, 2003, Dranitsaris *et al.*, 2009), clinical data (like baseline risk factors (personal history of disease (Karnon & Jones, 2003; Epstein *et al*., 2006; Dedes *et al.*, 2009), and patients age at diagnosis (Block, Putter, Bonnema, Hage, Bartelink & Velde, 2009; Palmer *et al*, 2004[a])), progression risk factors (invasion tumor type (Karnon & Jones, 2003; Kurian, Thompson, Gaw, Arai, Ortiz & Garber, 2007; Liberato, Marchetti e Barrosi, 2007; Karnon, Delea, Papo, Bargout, Thomas & Johnston, 2006; Epstein *et al*., 2006), tumor size (Block *et al.*, 2009) and lymphatic nodes affected (Block *et al.*, 2009)) and study perspective (Silva *et al*., 1998).

2.3.2.1.1. PATIENT NUMBER

The BC hospital/country patient number (depending on the adopted perspective) is very important for cost calculation and mainly for budget impact analysis. In fact, depending on the patient number, the scarce resources must be distributed in way to provide the best and equal care to all patients (Palmer *et al*, 2004[a]).

2.3.2.1.2. (NEW) TREATMENT PATTERNS TO BE TESTED

Genetic and epidemiological investigations provide means of detecting BC at an early stage or of identifying healthy individuals at risk of the disease. The prognosis for women with advanced BC varies widely, but in general the earlier is detected, the better the prognosis (Radice & Redaelli, 2003).

This part of the study covers information on new pharmacologic BC therapy opportunities, treatment effect and change of physiological parameters as a consequence of the treatment, which are compared to those of the most common treatment patterns.

The economic evaluation studies should present a discussion of therapeutic alternatives as well as a major justification for choice of the comparators used for analysis (Palmer *et al*, 2004[a]).
So in practice, we may include one or two terms of comparison:

- There will be one comparison term whenever the technology / medical strategy with the greatest number of users is both more efficient and has lower costs;
- Two comparisons should be considered when the more effective option doesn't match the most used but it is the one with the lowest cost; or when the more effective is the one that has lower costs, but it is not the most used.

The aim of this comparisons is to identify relevant alternatives that allow an assessment as closely as possible of the cost-opportunity of the new treatment under consideration. An alternative should be described as therapeutic class, brand name and common international name, dosage and mode of administration, approved therapeutic

indications and therapeutic indications for which the economic evaluation is carried out (Silva *et al*., 1998).

Currently, the major therapies for BC are surgery, radiotherapy and systemic cytostatic therapy (chemotherapy drugs, endocrine/anti-hormone drugs and immunomodulators).
Treatment choice varies according to a number of factors, including cancer stage, the presence of estrogen/progesterone receptors, of HER-2 and of *vascular endothelial growth factor (VEGF)*.

Treatments can be classified as local (primary BC) or systemic (after tumor removal and/or nodal and metastatic involvement).

Surgery of primary BC provides loco regional control of the disease. The trend for surgical techniques has been toward more conservative (less disfiguring) procedures that showed the same statistical survival (overall or disease-free) when compared with more mutilating treatments (Radice & Redaelli, 2003).

Radiotherapy of BC has been used as local therapy, generally as an adjuvant of surgery to aid controlling or preventing growth of residual tumor cells after surgery and to try to control metastatic disease. Radiotherapy, however, has its own acute and chronic complications, and it is associated with a small risk of development of secondary malignancies (Radice & Redaelli, 2003). It is usually preferred for patients with the highest risk of loco regional recurrence. In some cases, a radioactive substance is placed within the diseased tissues in thin plastic tubes. This technique of implant radiation is termed brachytherapy.

The use of **systemic cytostatic treatment** has become a more central element of therapy with the increasing recognition of the systemic nature of BC and the introduction of more effective regimens.
The treatment is different for early and advanced breast cancer. While the treatment aim of early BC is the cure, advanced BC is regarded as incurable and, despite treatment; total survival time is often less than a year. For these patients, palliation of symptoms,

minimizing adverse effects of therapy and maximizing quality of life are the major issues in selecting a treatment strategy.

Each treatment option has adverse events that can be life threatening or sufficiently serious to suggest treatment discontinuation in favor of an alternative, less toxic therapy. In fact, all treatment options affect patients' *health-related quality of life (HR-QOL)* in various ways. In particular, the use of antineoplasic agents has a large impact on patients' HR-QOL (Radice & Redaelli, 2003).

In this study we will consider the difference between two different systemic, antineoplasic therapies in women with BC, after surgery and radiotherapy cycles completed, this last if adequate.

As new therapy to be tested, we will take into account the administration of paclitaxel plus bevacizumab in BC stages III and IV, as an alternative therapy solution through the oncologist perspective. In fact, this same therapeutical option is still being tested to IPOL hospital formulary insertion, in our days, which makes it opportune to analyze.

Bevacizumab, is a monoclonal antibody designed to attach to VEGF, a protein that circulates in the blood and makes blood vessels grow. A study of Yoshiji, Gomez, Shibuya & Thorgeirsson (1996) compared gene expression of VEGF and other pro-angiogenic factors in paired breast carcinomas and noncancerous breast tissue. It showed that there was a large difference in VEGF expression between cancerous tissue and normal tissue, achieving an **increase of expression of 6,5 times in abnormal breast tissue.** This result was corroborated by the study of Konecny, Meng, Untch, Wang, Bauerfeind, Epstein, Stieber, Vernes, Gutierrez, Hong, Beryt, Hepp, Slamon & Pegram (2004), wich showed that the majority of breast tumors overexpressed either of two isoforms of VEGF—VEGF165 or VEGF121. The investigators also examined the relationship between VEGF expression and other important factors such as HER-2 status and lymphatic nodes involvement, as shown in the table below.

Variables	Positive for $VEGF_{165}$	Positive for $VEGF_{121}$
Overall	74% (453/611)	59% (359/611)
HER-2		
Negative	71% (353/497)	55% (271/497)
Positive	88% (100/114)	77% (88/114)
Lymph nodes		
Negative	72% (210/290)	53% (155/290)
Positive	75% (233/310)	63% (196/310)
Hormone receptor status		
Negative	80% (109/137)	73% (100/137)
Positive	72% (343/474)	55% (259/474)
Histology		
Invasive ductal	78% (432/554)	61% (340/554)
Invasive lobular	22% (8/37)	19% (7/37)

Table n. 5: Breast tumor characteristics and VEGF expression.
Source: Adapted from Konecny *et al.* (2004).

From this results we can conclude that there isn´t any significant correlation between the expression of VEGF receptors and lymphatic nodes affected, although associated with a higher probability with HER-2 positive and ER negative BC.

By attaching to VEGF, Bevacizumab stops it having an effect. As a result, the cancer cells cannot develop their own blood supply and are starved of oxygen and nutrients, helping to slow down the growth of tumors. The most common side effects in patients receiving Bevacizumab are **febrile neutropenia**, leucopenia, thrombocytopenia, neutropenia, **arterial thromboembolism**, neuropathy, **diarrhea**, headache, eye disorders, dyspnoea, epistaxis, gastrointestinal perforations, rectal hemorrhage, exfoliative dermatitis and **arthralgia** (EMEA, 2010).

The dose we will study is of 10 mg per kilogram body weight, **every three weeks, at least for one year** if therapy doesn´t have to be interrupted taking into account the toxicity associated with the active substance. Considering a medium body weight of 65kg, we will chose to simulate an **administration of 650mg of bevacizumab through an infusion during around 90 minutes,** for one year (EMEA, 2010).

Paclitaxel is an antimicrotubule agent that promotes union of microtubules from tubulin dimmers and stabilizes microtubules preventing depolymerization. This stability leads to inhibition of normal dynamic reorganization of the microtubule network, which is essential for vital cellular functions in interphase and mitosis. In addition, paclitaxel induces abnormal clusters or bundles of microtubules in the cell cycle and multiple formations of radial microtubules during mitosis, preventing replication and division of tumor cells. The recommended dose of paclitaxel is **175 mg/m^2 administered over a period of 3 hours, in a total of 4 cycles, with a 3-week interval between cycles**. Severe **neutropenia, cardiovascular toxicity**, peripheral neuropathy, **arthralgia** and increased likelihood of pneumonia are the major adverse effects to have into consideration (INFARMED, 2010).

Note that the INFARMED and/ or EMEA (European Medicines Agency) Public Assessment Reports of the described medicines are available at **Appendix N. 4**.

As a summary, we can analyze the following table:

Receptors	BC Stage	Active substance	Therapy length	ARF	AHF	APD	ACVE	Ost	AA	AC	AD	Global /Major Side Effects
VEGF +	**III**	Paclitaxel	4 month			√	√√		√	√√		APD, **ACVE**, AA, **AC**
		Bevacizumab	12 month						√	√√	√√	AA, **AC, AD**

Legend: ARF-acute renal failure; AHF-acute hepatic failure; APD-acute pulmonary disease; ACVE-acute cardiovascular event; AA-acute arthralgia; AC-acute cytopenia; Ost – Osteoporosis.

Table n. 6: Illustrating major new therapy side effects, according to disease stage and tumor type.
Major side effects of each therapy cycle are darker high lightened.
Source: Own construct.

2.3.2.1.3. CLINICAL DATA

2.3.2.1.3.1.1. BASELINE RISK FACTORS:

PERSONAL HISTORY OF DISEASE AND PATIENTS AGE AT DIAGNOSIS

The previous personal history of disease(s), namely the ones that can be triggered or that can result in acute events possibly fatal, considering drug antineoplasic systemic therapy side effects, are essential to consider (Dedes *et al.*, 2009). In this study is therefore important to define the history of cardiovascular, pulmonary, renal, hepatic, intestine, reumathological, hematological and of osteoporosis previous disease(s).

On the other hand, patients age at diagnosis is of extreme importance because it will positively and strongly influence the way patients handle therapy adverse effects, and the disease transition probabilities that make part of the Markovs process sisease progression model and that reflect age specific life expectancy/mortality rates (Sonnenberg & Beck, 1993). This idea is shared by most authors, considering at least three age intervals (Block, 2009). Unfortunately, due to scarcity of Portuguese data, we were subject to the use of only two age intervals, that we consider misfits, as described latter.

The patient's age intervals at diagnosis regarding the model construction are from 24 to 64 years old and more than 65 years old.

2.3.2.1.3.1.2. PROGRESSION RISK FACTORS:

TUMOR TYPE, TUMOR SIZE AND LYMPHATIC NODES AFFECTED

The tumor type, tumor size and the number of lymphatic nodes affected at diagnosis are important prognostic and predictive factors in BC, which will define the disease stage and the therapy to be prescribed and administrated.

Regarding tumor type, note the importance of diagnosing the presence of HER-2, since about **25% of BC patients are estimated to have HER-2–positive breast carcinomas** (Radice and Redaelli, 2003). The **ER is also essential and is usually negative when**

HER-2 is positive and positive when the same receptor is negative (in about 75% of BC patients (EMEA, 2010)).

The tumor size and the number of lymphatic nodes affected vary in direct proportion with the disease stage and severity, and have huge reprocursions in BC stage.

2.3.2.1.5. STUDY PERSPECTIVE

The objectives and hence the original question generally reflect the interests of the entity who orders the study, resulting in a selection of data (costs and consequences) to be included in the analysis. Therefore, we must give utmost importance to the perspective of the study we will use (Silva *et al.*, 1998). In this case, we will consider the M*inistry of Health, the Hospital and Physicians perspectives*, which involve the consequences to patients and costs to public health funders (namely the NHS) or to public/private hospitals, respectively. Note that for all of these perspectives, only direct related costs to each entity are included in economic evaluations (Silva *et al.*, 1998).

2.3.2.2. DATA PROCESSOR

The **data processor** stores pre-existing data from published sources of clinical and economic studies. These are usual treatment patterns; incidence and prevalence of the disease in the country, female population number, cancer/health budget; time horizon of the study, cycle length, probability of developing a complication/adverse drug effect, probability of progressing to the next level of disease severity, or of dying (which includes mortality rate specific from BC and from BC non-specific mortality rate, this last one based on country-specific mortality statistics), direct costs (clinical and drug costs, including costs of ongoing disease complications and costs of acute events), quality of life data (associated with disease stages) and country-specific discount rate. The product of these variables is a Markov Decision Process Matrix Model, required to perform each simulation, as we shall see through this chapter.

Note that according to the Portuguese Guidelines for Economic Evaluation of Medicines Studies of Silva *et al.* (1998), the economic evaluation of therapeutic strategies should refer to the actual population, which will target these strategies in the context of current clinical practice. The target population must be clearly described, including the indication of the prevalence, diagnosis, severity of illness, age and distribution by gender. Other factors that may be relevant are the rates of mortality, the presence or absence of co-morbidity, rates of adherence to treatment and of distribution of the disease by geographic areas and socioeconomic groups. This is particularly relevant in modeling systems. The target population can be divided into a small number of subgroups (with different demographic or clinical characteristics). However, subgroup analysis is vulnerable to bias, manipulation and loss of statistical power due to reduced sample, which implies.

2.3.2.2.1. MOST COMMON TREATMENT PATTERNS

The long-term treatment pathway is represented by the scheme presented below, which reflects common practice in Portugal, according to the **therapeutic protocols most commonly used to treat early and metastatic breast cancer** in the *Portuguese*

Institute of Oncology of Lisbon (IPOL), the biggest specialized hospital in the country with around 11.500 patients per year.

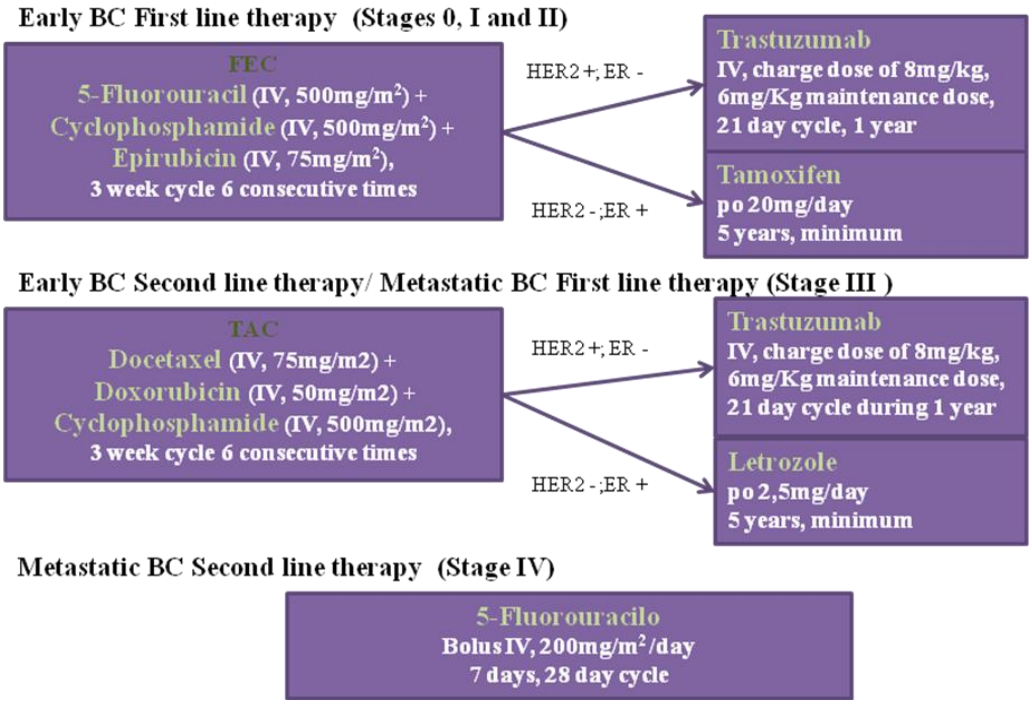

Figure 6: Most Currently Used Treatment Protocols, 2010.

Data source: Own Construct.

For **first line therapy in early breast cancer**, is used the **FEC** (5-fluorouracil (500mg/m^2) + Cyclophosphamide (500mg/m^2) + Epirubicin (75mg/m^2), a 3 week cycle that is commonly done 6 consecutive times) **followed by Trastuzumab** (a 21 day cycle, with charge dose of 8mg/kg, followed by a 6mg/Kg maintenance dose, during 1 year), if the patient as a increased or over-expression of HER-2 receptor (HER-2+), usually ER-; **or by Tamoxifen** (20mg/day orally, during 5 years minimum), if the patient is HER-2 - and usually ER +.

Note that in older patients (65 and plus) and/or with high incidence of co-morbidities, the first line therapy is AC (Cyclophosphamide (600mg/m^2) + Doxorubicin (60mg/m^2), a 3 week cycle), followed by FEC if the patient do not respond to AC; and that if surgery is not advised, Docetaxel (100mg/m^2, 3 week cycle) is used until tumor reduction. On the other hand, third-generation aromatase inhibitors (AIs) – anastrozole (ANA, intramuscular administration), letrozole (LET, oral administration) and exemestane (EXE, oral administration) – may also be used in adjuvant treatment of ER+

hormone-sensitive early breast cancer for at least 5 years. However, since these are not the procedures most commonly used, they will not be considered in this study.

For **second line therapy**, used if the patient is not responding to first-line therapy for early breast cancer and the disease is progressing or for **metastatic breast cancer** is used the **TAC** (Docetaxel (IV, 75mg/m^2) + Doxorubicin (IV, 50mg/m^2) + Cyclophosphamide (IV, 500mg/m^2), a 3 week cycle for 6 consecutive times) **followed by Trastuzumab** (IV, a 21 day cycle, with charge dose of 8mg/kg, followed by a 6mg/Kg maintenance dose, during 1 year), if the patient is HER2 +.
Isolated chemotherapy with Paclitaxel (IV, 80mg/m^2, weekly administered) or with Docetaxel (IV, 100mg/m^2, 3 week cycle) is also used to the same effect but less frequently so, it will also not be considered.

For **third line medicines, dedicated to palliative care,** is used **5 – Fluorouracil** (IV, 200mg/m^2/day, in continuous infusion) or **Vinorelbine** (IV, 30mg/m^2, administered at days 1, 8 and 15 of the cycle), but as this last option is less currently used, we will only consider the first one for model construction.

These treatment protocols were investigated through the analysis of 200 charts of cytostatic drugs therapy protocols prepared in 2010 at the Pharmacy of the IPOL.
A prototype of these can be consulted in **Appendix n. 5**.

Chemotherapy drugs used in systemic treatment are classified based on how they work.

Alkylating drugs kill cancer cells by directly attacking DNA, the genetic material of the genes. **Cyclophosphamide** is an alkylating drug from the oxazaphosphorin group, chemically related to nitrogen mustard. It is activated in the liver and its cytotoxic action is based on an interaction between its alkylating metabolites and DNA. This alkylation results in the breaking and linking of strands of DNA and protein-DNA cross links. The major adverse effects of Cyclophosphamide are myelosuppression, which involve leukopenia, thrombocytopenia, and anemia; induced secondary cardiomyopathy manifested as arrhythmia, *electrocardiogram (ECG)* and *left ventricular ejection*

fraction (LVEF) changes; and risk of developing cancer in the urinary tract (Infarmed, 2010).

Antimetabolites interfere with the production of DNA and keep cells from growing and multiplying. An example of an antimetabolite is **5-fluorouracil (5-FU)**, an analogue of uracil, a component of ribonucleic acid. After intracellular conversion to active deoxynucleotides, interferes with DNA synthesis by blocking the conversion of the acid from desoxiuridilic into timidilic made by the cellular enzyme thymidylate synthetase. The 5-Fluorouracil may also interfere with the synthesis of RNA. The major side effects are stomatitis /mucositis, diarrhea, and bleeding from the gastrointestinal tract; chest pain, tachycardia, ECG changes, thrombophlebitis; leukopenia, neutropenia and thrombocytopenia (Infarmed, 2010).

Docetaxel belongs to the group of anticancer medicines known as the *Taxanes.* Docetaxel blocks the ability of cells to destroy the internal 'skeleton' that allows them to divide and multiply. Docetaxel also affects non cancer cells such as blood cells, which can cause side effects including neutropenia, anemia, thrombocytopenia, febrile neutropenia; neuropathy; stomatitis and diarrhea (EMEA, 2010).

Antitumor antibiotics are made from natural substances such as fungi in the soil. They interfere with important cell functions, including production of DNA and cell proteins. **Doxorubicin Hydrochloride** belongs to this group of chemotherapy drugs, also called *anthracyclines*. It works by interfering with the DNA within cells, preventing them from making more copies of DNA and proteins. This means that cancer cells cannot divide and eventually die. Doxorubicin accumulates in areas in the body where the blood vessels have an abnormal shape, such as within tumors, where its action is concentrated. The most common side effect seen is nausea, but others include stomatitis low blood cell counts, loss of appetite, diarrhea and mucositis (inflammation of the mouth and throat) (EMEA, 2010).
Similarly to other anthracyclines, **Epirubicin** acts by intercalating DNA strands. Intercalation results in complex formation which inhibits DNA and RNA synthesis since the intercalation of Epirubicin also seems to interfere with the "cleavable complex" of DNA topoisomerase. Epirubicin also generates free radicals and the

formation of chelates with metal ions that cause cell and DNA damage. Epirubicin is favored over Doxorubicin as it appears to cause fewer side-effects. Adverse events commonly observed after intravenous administration are myelosuppression, gastrointestinal disorders and heart disease. Myelosuppression occurs mostly in the form of leukopenia and /or granulocytopenia (neutropenia). Often occurs mucositis (mainly stomatitis); vomiting and diarrhea can cause severe dehydration. Moreover, there may be two forms of cardiotoxicity: in the immediate type characterized by arrhythmia and /or ECG not specific changes; and in the delayed-type, which comes in the form of myocardial damage that manifests itself through symptoms of congestive heart failure (Infarmed, 2010).

A new range of *Aromatase Inhibitors* has reached clinical use in the last few years. These molecules inhibit the aromatization of androgens and estrogens in peripheral tissues, inhibiting tumor progression. It includes **Exemestane**, which is a steroidal compound, and **Anastrozole** and **Letrozole** which are no steroidal molecules. Anastrozole and letrozole show better tolerance and efficacy, however, Letrozole is the one with fewer side effects (Radice and Redaelli, 2003).
The suppression of growth stimulation mediated by estrogen is a pre-requisite for tumor response in cases where the growth of tumor tissue depends on the presence of estrogen. The suppression this hormone biosynthesis in peripheral tissues and in the cancerous tissue itself can be achieved by specific inhibition of the enzyme aromatase. **Letrozole** is an extremely specific no steroidal aromatase inhibitor. Note that there was no observation of steroids production reduction in adrenal level, there was also no changes in plasma androgens (testosterone and androstenedione) or in plasma levels of luteinising hormone (LH) and follicle-stimulating hormone (FSH). The same occurs with thyroid function. Generally, adverse reactions are mainly mild or moderate and can be attributed to the normal pharmacological consequences associated to estrogen deprivation, such as hot flushes, arthralgia, and myalgia. There is also a higher incidence, but not significant, of osteoporosis and bone fractures (Infarmed, 2010).

When substances act on the cytoplasm receptors of hormones, they behave as *anti-hormones* that slow the growth of some cancers that depend on hormones.

Tamoxifen is a potent estrogen antagonist at the level of its receptors in breast tissue, and is used to treat breast cancers that depend on the hormone estrogen for growth. Tamoxifen is a no steroidal substance that is still the agent of choice in the first-line treatment of patients with advanced hormone-sensitive disease. However, its leading position is threatened currently by the new AIs and, in the future, by the newer selective estrogen receptor modulators and estrogen receptor down regulators that are still in development (Radice & Redaelli, 2003). Note that Tamoxifen is usually well tolerated but is associated with an increased risk of Thromboembolism and of endometrial carcinoma. Side effects that have been reported are mainly due to anti-estrogen action of the drug, like vaginal bleeding, vulvar pruritus, and headache. However, cases of leukopenia, sometimes associated with anemia and /or thrombocytopenia, as well as alterations in the levels of liver enzymes had also been found (Infarmed, 2010). Furthermore, tumors inevitably become resistant to Tamoxifen after a period of time, and there is a need for effective and tolerable alternatives that do not is not show cross-resistance with tamoxifen in advanced disease (Radice & Redaelli, 2003).

Immunomodulators are drugs known as biologic response modifiers. **Trastuzumab** is a humanized monoclonal antibody. A monoclonal antibody is an antibody (a type of protein) that has been designed to recognize and attach to a specific structure (called an antigen) that is found on certain cells in the body. Trastuzumab has been designed to attach to HER-2 – the first BC antigen-specific therapy for HER-2–positive breast carcinomas (Radice & Redaelli, 2003). Attaching trastuzumab to HER-2, activates cells of the immune system, which then kill the tumor cells. Trastuzumab also stops HER-2 producing signals that cause the tumor cells to grow. About a quarter of breast cancers over express HER-2 (EMEA, 2010). It had begun a new era in cancer management, the first pharmacogenomically-derived drug to enter the market. Its application requires physicians to determine patient's genotype before deciding which patient may benefit most from the treatment. A number of ongoing trials are investigating the combination of trastuzumab with major chemotherapy regimens (e.g. anthracyclines, Taxanes, platen derivatives) in the advanced disease and adjuvant setting.

The most common side effects with trastuzumab (seen in more than 1 patient in 10) are febrile neutropenia and cardiotoxicity (including heart failure, palpitations (a rapid or irregular heartbeat) and cardiac flutter (rapid contractions of the heart). Cases of

dyspnoea (difficulty breathing), diarrhea, arthralgia (joint pain), muscle tightness, myalgia (muscle pain), asthenia (weakness) were also registed (EMEA, 2010).

Note that the INFARMED and/ or EMEA (European Medicines Agency) Public Assessment Reports of the described medicines are available at **Appendix N. 6.**

To turn easier to analyze the main adverse effects of each substance that were contemplated in the model (considering their degree of severeness and life threatening), we built the following table:

Tumour Receptors	Stages	Active substance	Therapy length	ARF	AHF	APD	ACVE	Ost	AA	AC	AD	Global Side Effects
HER+ ER-	**0, I and II**	5-Fluorouracil	6 month				√			√		ARF, **ACVE**, **AC**, AD
		Cyclophosphamide		√			√			√		
		Epirubicin					√			√	√	
		Trastuzumab	12 month			√	√√		√	√√	√	APD, **ACVE**, AA, **AC,** AD
	III	Docetaxel	6 month							√√	√	ARF, ACVE, **AC**, **AD**
		Doxorubicin								√	√	
		Cyclophosphamide		√			√			√		
		Trastuzumab	12 month			√	√√		√	√√	√	APD, **ACVE**, AA, **AC,** AD
	IV	5-Fluorouracil	Until death				√			√		ACVE, AC
HER ER+	**0, I and II**	5-Fluorouracil	6 month				√			√		ARF, **ACVE**, **AC**, AD
		Cyclophosphamide		√			√			√		
		Epirubicin					√			√	√	
		Tamoxifen	60 month		√		√			√		AHF, ACVE, AC
	III	Docetaxel	6 month							√√	√	ARF, ACVE, **AC**, **AD**
		Doxorubicin								√	√	
		Cyclophosphamide		√			√			√		
		Letrozole	60 month					√	√			Ost, AA
	IV	5-Fluorouracil	Until death				√			√		ACVE, AC

Legend: ARF-acute renal failure; AHF-acute hepatic failure; APD-acute pulmonary disease; ACVE-acute cardiovascular event; AA-acute arthralgia; AC-acute cytopenia; Ost – Osteoporosis.

Table n. 7: Illustrating major current therapy side effects, according to disease stage and tumor type.
Major side effects of each therapy cycle are darker high lightened.
Source: Own construct.

Pre-medication (namely dexamethasone and furosemide) is often used to reduce the incidence and severity of adverse effects of chemotherapy, but since the costs with this drugs are a lot less than the cost of every cytostatic drugs, and that they are frequently used in combination with any of the chemotherapy agents, they were not considered in the model. However, for a brief further information, please consult **Appendix n.7**.

Neo-adjuvant therapy, such as an anthracycline-containing regimen or hormonal therapies are given as preoperative or primary treatment before loco-regional therapy to decrease the tumor bulk, thereby down staging the disease. However this isn´t this study main focus.

The CHEUAL BC model takes only into consideration after surgery and eventually after radiotherapy systemic cytostatic drug treatment or when surgery/radiation are no longer viable options.

The model will determine the progression of the physiological parameters over time based on equations taken from published data or as fixed incremental adjustments every year (in the absence of any relevant published data).

2.3.2.2.2. BC INCIDENCE AND PREVALENCE

Taking into account what is shown in the picture bellow, **the number of Portuguese female breast cancer cases** (4,309 per 100.000 people) **in 2002 was very low (3,24%)** when compared to the EU Countries average incidence value (132,91 per 100.000). Following the same tendency, **Portuguese BC incidence gross rate (82,8 per 100.000 people) was only 80,0% of the EU average value**, which supports the idea that BC incidence is lower in Portugal than in the rest of the European members. However, the **age standardized Portuguese rate incidence was of 55,5 years old**, while in the average EU was of 66,75years, meaning that Bc was appearing approximately eleven years earlier in Portugal than in the rest of the European countries.

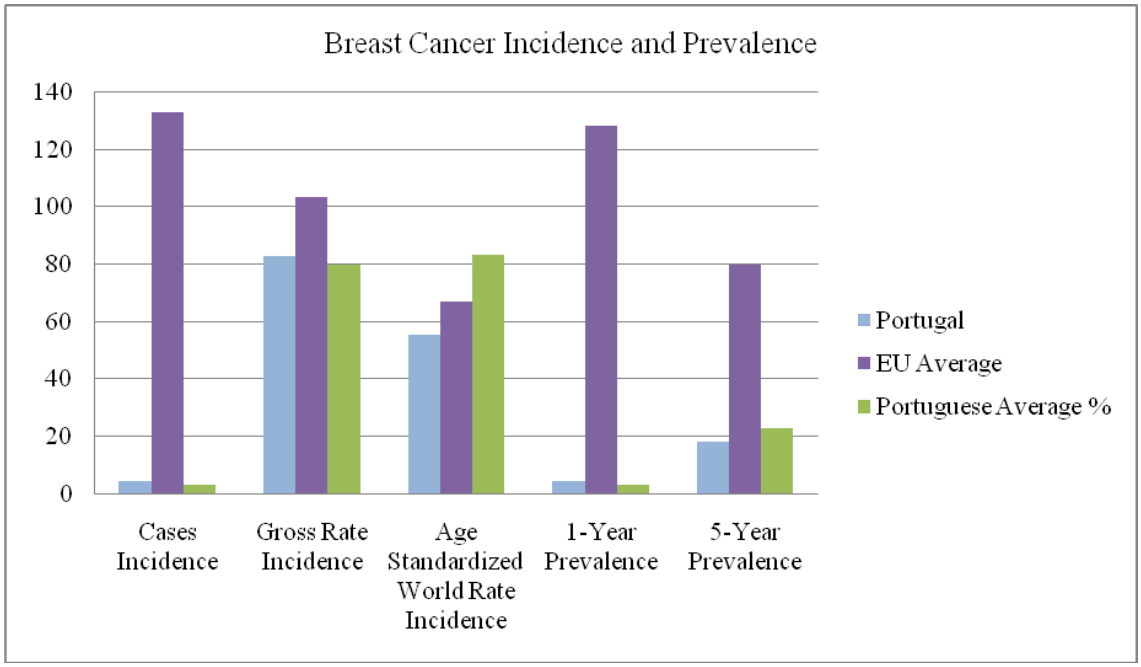

Chart n. 6: Relationship between Portuguese and Average EU data about Female BC Incidence (Gross and ASW rates per 100.000 people) and Prevalence.

Source: Own construct based on data provided by IARC - GLOBOCAN 2002.

Likewise, Portuguese female data of 1-year prevalence and of 5-years prevalence, show a very low percentage (3,32% and 22,95%, respectively) of BC prevalence when compared to EU average data. This indicates that the number of Portuguese people suffering from the disease is very low when compared to other European countries. As we didn´t find more recent data, we will consider this statistics in our model construction.

2.3.2.2.3. COUNTRY DATA: FEMALE POPULATION NUMBER AND HEALTH BUDGET

Our research led us to the country female population data in 2009, as it can be appreciated in the next table. This data is important to extrapolate probable patient number, considering BC incidence and prevalence data.

Sex	Age Group	Population Number	Percentage
Male and female	Total	10637713	100,00
	0 - 14 years	1616617	15,20
	15 - 24 years	1181435	11,11
	25 - 64 years	5938508	55,83
	65 and plus	1901153	17,87
Male	Total	5148203	48,40
	0 - 14 years	828733	7,79
	15 - 24 years	602821	5,67
	25 - 64 years	2923237	27,48
	65 and plus	793412	7,46
Female	**Total**	**5489510**	**51,60**
	0 - 14 years	787884	7,41
	15 - 24 years	578614	5,44
	25 - 64 years	**3015271**	**28,35**
	65 and plus	**1107741**	**10,41**

Table n. 8: 2009 Annual Number Portuguese by Age Group and Sex.

Source: INE, May 2010.

This data suggests age grouping with the same intervals as presented above, in order to simplify the model development and to analyze comparable data. This means that from this table, we will only consider that there were 3015271 women within **25-64 age group and** 1107741 women within the **65 and more group, corresponding to** 28,35% and to 10,41% of the Portuguese population, respectively; and to **54,93% and 20,18% of female gender population, respectively**.

However, these two age intervals weren´t the ones we would ideally chose to do this research. Remember that we had already seen that the age standardized world rate incidence was of 55,5 years in Portugal, while in the average European Countries was of 66,75years, wich are very different considering life expectancy and probability of developing complications (namely related to chemotherapy adverse effects and previous disease history). Note that the interval between 25 and 64 years old is too large to reflect these considerations.

After analyzing female population number evaluation and disease incidence, is important to analyze which health resources we have and will have in the country, for the year that has just started.

Along the necessity of implementing austerity measures to reduce the country's liabilities, advised by the EU, and according to the proposal of the *National State Budget (NSB)* for 2011, the Ministry of Health leads the spending cuts, with a decrease of 7 percent of the expense, from around 8 860 to 8 250 million Euros from 2010 to 2011, as it can be analyzed from the following table:

Table n. 9: Integrated Services Expenditure by Organizational Classification, Specified by Chapters: Heath; Source: National State Budget to 2011.

Organic Designation	Expense by Chapter 2010	Expense by Chapter 2011
Office of Government Members	3 248 861€	2 952 894€
Central Services of the Ministry of Health	49 840 115€	46 716 089€
Health Care Intervention	8 771 454 365€	8174101013€
Investment Plan	34 071 930€	26 060 614€
Minister of Heath	8 858 615 271€	8 249 830 610€

To achieve this goal, the State counts with the implementation of various measures of restraint (NSB Data from 2010 and to 2011).

Regarding the following table, we can also analyze that the European Community Fund supports a little more than half of the health related expense, which strengthens the fact that a national effort is urgent do decrease the expenditure.

Table n. 10: Investment and Development Expenditure Programme of the Central Administration (PIDDAC) – Ministry of Heath
Source: National State Budget to 2011: Ministry of Finance and Public Administration / Department of General Budget (MFAP / DGO)

Funding Source (*in Euros)*		Years Before	2011
National Funding		37 535 569	25 600 000
	General Revenue	37 424 931	25 600 000
	Own Revenue	110 638	0
European Union Community Funding		47 490 957	28 560 572
	Feder QCA III e PO*	47 412 163	28 483 043
	Social European Fund	78 794	77 529
Total		85 026 526	54 160 572

Legend:
* Feder QCA III- European Funf for Regional Development of the Community Board of Support III; PO – Operational Programs.

In the next table we present the expected expense by the major public health entities and we can get some idea of the weight of each in the heath burden.

Table n.11: Expenditure by Autonomous Funds and Services by Organic Classification with Specification of Global Expense for Each Service and Fund: Heath
Source: National State Budget to 2011.

Designation	Expense (*in Euros)*
Central Heath Administration System, IP	8 066 245 743
Regional Health Administration of Lisbon and Tejo Valley, IP	1 348 199 591
Regional Health Administration of Alentejo, IP	185 956 617
Regional Health Administration of Algarve, IP	160 499 767
Regional Heath Administration of the Center, IP	643 359 166
Regional Heath Administration of the North, IP	1 378 341 496
Histocompatibility Center of the Center	2 460 155
Histocompatibility Center of the North	4 315 238
Histocompatibility Center of the South	6 947 742
Cascais Central Hospital	7 920 917
Torres Vedras Central Hospital	34 638 156
West North Central Hospital	45 378 931
Psychiatric Central Hospital of Coimbra	19 482 745
Psychiatric Central Hospital of Lisbon	35 771 452
Rehabilitation Medical Center - Rovisco Pais	7 118 772
Health Authority Regulation	4 695 239
Arcebispo João Crisóstomo Hospital- Cantanhede	4 809 493
Cândido de Figueiredo Hospital – Tondela	6 501 756
Joaquim Urbano Hospital	17 613 359
Pombal Hospital	6 966 427
S. Marcos Hospital – Braga	19 992 122
Águeda district Hospital	12 922 059
Dr. Zagal Francisco Hospital – Ovar	8 781 315
José de Castro Luciano Hospital – Anadia	5 715 646
N. Sra. Conceição Hospital – Valonfo	7 659 275
Reynaldo dos Santos Hospital – Vila Franca de Xira	30 117 741
Visconde de Salreu Hospital – Estarreja	6 369 165
INEM-National Institute for Medical Emergency	82 335 508
INFARMED - National Authority of Medicines and Health Products, IP	42 882 430
Dr. Ricardo Jorge National Institute of Heath	35 788 106
Dr. Gama Pinto Ophtalmologycal Institute	7 402 994
Portuguese Blood Institute	75 007 621
Dr. Alfredo da Costa Maternity	26 180 888

However, IPOL is not included in the table because it had been transformed into a public corporate entity (EPE) with ward of the state. The main source of revenue for EPE hospitals is generated by the NHS (approximately 75% in IPOL, as it can be seen in the next table, of IPOL production plan to 2011).

	Global Production	NHS Production	% NHS Patients
External Appointments			
Total Appointments	199865	151898	76,00
First Appointments	38560	29645	76,88
Subsequent Appointments	161305	122253	75,79
Internment			
Outgoing patients – acute	9806	7536	76,85
Medical GDH	6449	5026	77,93
Cirurgical GDH	3357	2511	74,80
Programmed cirurgical GDH	3008	2251	74,83
Urgent cirurgical GDH	349	260	74,50
Nursing home patients (IPO)	2969	2387	80,40
Nursing home patients (IPO)	17533	13693	78,10
Paliative care			
Daily hospital sessions			
Hematology	15190	11681	76,90
Immuno-hemoterapy	2250	1540	68,44
Other	6791	5190	76,42
Home services			
Total home visits	2591	1979	76,38
Ambulatory GDH			
Medical GDH	106957	84469	78,97
Cirurgical GDH	2805	2124	75,72
Management system for patients registered for surgery (SIGIC) additional production			
Cirurgical GDH	1202	899	74,79
Ambulatory Cirurgical GDH			

Table n. 12: IPOL Production Plan to 2009.
Source: 2008 IPOL Accounts Report.

The remaining revenue base is ensured by the sub-health systems, insurers and private companies. The lines of activity considered are the internment discharges, external appointments, session in the daily hospital and episodes of urgency. According to the latest accounts report of the IPOL (from 2008) provided by the Ministry of Health, the hospital's operating income registed a loss of 5 million Euros, result worse than in 2007, were the income statement described a loss of three million and six hundred thousand Euros, as it is shown bellow.

Rubric	2007 (million Euros)	2008 (million Euros)	Variation %
Operating Income (A)	110,2	114,1	3,9
Operating Costs (B)	108,6	113,6	5
Gross Operating Surplus (A-B)	1,6	0,5	-1,1
Depreciation and Provisions (C)	-5,2	-5,6	-0,4
Operating Results (A-B-C)	-3,6	-5,1	-1,5
Financial Results (D)	2,4	2,2	-0,2
Extraordinary Results (E)	2,8	3,9	1,1
Results Before Taxes (A-B-C+D+E)	1,6	1,0	-0,6
Tax for the Year (F)	-1,1	-0,5	0,6
Net results (A-B-C+D+E-F)	0,4	0,4	0

Table n.13: IPOL Economical Performance, 2008
Source: 2008 IPOL Accounts Report.

Following the same source, we realize that personnel costs (46%) and drug costs (24%) represent about 70% of the operating costs. Supplies are made by pharmaceuticals (85%), medical consumables (13%), hospitality (0.95%) and administrative consumptions (0.54%), and by equipment maintenance and servicing (0.51%). The group of antineoplasic drugs represents 65% of total consumption of medicines.

Unfortunately, we couldn´t find any data related specifically to breast cancer expenses or number of patients, because the hospital isn´t differentiating them yet per specific type of cancer. We hope it will in the near future, aid by the hospitals software actualization started last January (of 2011), in order to turn easier the investigation of specific disease costs and patient number.

2.3.2.2.4. BC SPECIFIC AND NON-SPECIFIC MORTALITY RATES

The CHEUAL BC model allows **open cohort simulations**, incorporating population dynamics, whereby a prevalent cohort is defined at baseline, and patients both leave the simulated population (by dying) or join them (by adding incident patients to the BC population in question). **Note that the simulated population size may actually increase, if BC incidence rate is higher than the annual mortality rate within the population**, as in the study of Palmer *et al.* (2004[a]).

Data from the Health General Directorate reported in the Information Bulletin of the *High Commissionaire of Health (ACS)* in 2009, show that between 1999 and 2005 there has been registered a rising of the global mortality rate for both genders in Portugal. Male number of deaths grew from 11747 to 12792 (8,2%) and female from 8232 to 8875 (7,2%).

Considering that according to data previously presented, there are in Portugal 5.489.510 woman, and that the proportion between female population and female mortality rate was kept invariable since 2005, the female mortality tax was of 0,16% of female population, in 2005.

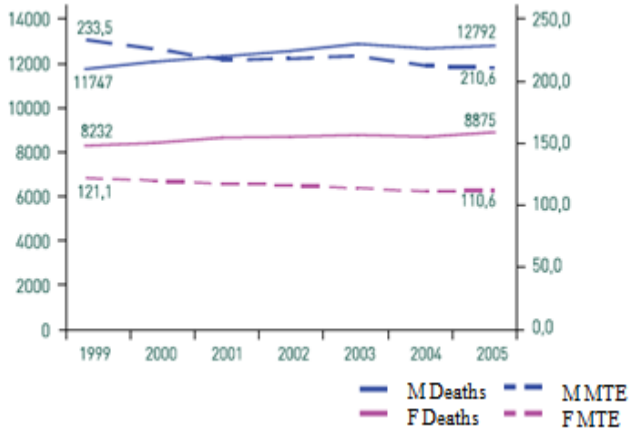

Chart n. 7: Portuguese main land number of death and standardized by age (/100000 people) cancer related mortality tax evolution (MTE).

Source: DGS, "O Risco de Morrer em Portugal – 1999 a 2005 [The risk of dying in Portugal – from 1999 to 2005]".

On the other hand, the Portuguese cancer related mortality rate has fallen between 1999 and 2005, from 233,5 to 210,6 per 100000 people for men, and from 121,1 to 110,6 per 100000 people for woman.

More recent data, specifically related to *breast cancer related mortality rate (BCRMR)* can be seen in the chart bellow (Chart n. 7) (Carrilho, 2009).

Analyzing it, we can see that BCRMR in men is negligible (approximately zero) in all the time stages. This is the reason why we have decided to address only female statistics

related to BC and to devote the CHEUAL BC model to women around the world, since their the main target of the disease.

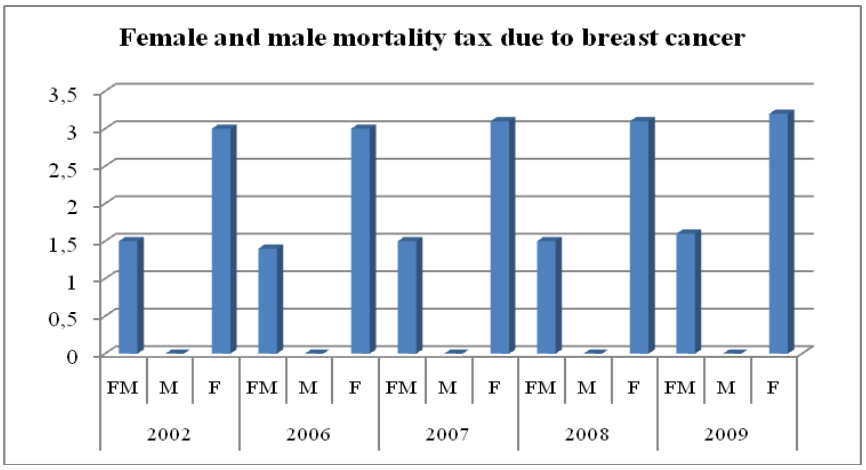

Chart n.8: Portuguese Population Female and Male Mortality Rate due to BC, considering time evolution. Source: Portuguese Statistics, Health Statistics 2002 -2009 (Carrilho, 2009).

Regard that female BCRMR has been slightly increasing since 2002, similarly to what has been happening to female and male BCRMR. To our model, we will consider the more updated data available. This means that we will develop our model based on the assumption that **female BCRMR is of 3,1% of all female number of deaths registered in the year 2009.** The 2009 global mortality rates are presented in the following table:

	Deaths 1st semester 2009			Deaths 2nd semester 2009			Total number of deathes 2009		
Age Groups	Total	%	%	Total	%	%	Total	%	%
20 - 24 years	38	0,18	-	53	0,24	-	91	0,21	-
25 - 29 years	40	0,19		65	0,29		105	0,24	
30 - 34 years	87	0,4		97	0,43		184	0,42	
35 - 39 years	164	0,76		164	0,73		328	0,74	
40 - 44 years	245	1,13		219	0,97		464	1,05	
45 - 49 years	332	1,54		364	1,62		696	1,58	
50 - 54 years	487	2,26		485	2,15		972	2,2	
55 - 59 years	588	2,72		570	2,53		1158	2,62	
60 - 64 years	888	4,11	**6,25**	830	3,68	**6,53**	1718	3,89	**12,78**
65 - 69 years	1243	5,76		1126	5,00		2369	5,37	
70 - 74 yerars	2142	9,92		1957	8,68		4099	9,29	
75 - 79 years	3686	17,06	**42,68**	3278	14,55	**44,54**	6964	15,78	**87,22**

80 - 84 years	3469	16,06		4813	21,37	8282	18,77	
85 - 89 years	2603	12,06		4036	17,92	6639	15,05	
90 - 94 years	3783	17,52		3054	13,56	6837	15,5	
95 - 99 years	1547	7,17		1201	5,33	2748	6,23	
100 - 104 years	230	1,07		201	0,89	431	0,98	
105 - 109 years	19	0,09		14	0,06	33	0,08	
Total	21591			22527		44118		
Total (%)	**48,9**	100		**51,1**	100		100	**100**

Table n. 14: 2009 Annual Number of Female Mortality Rate by Age Group and Semester.
Source: Adapted from INE, 2009

Considering the Portuguese female mortality rate table previously presented, we decided to despise the age interval of 20-24 years, since this has one of the lowest weight (of only 0,21%) in the total mortality rate considered, not having great importance in the overall result, and that we had chosen our patients age at diagnosis according to data previously presented in this thesis.

Adding the total death number in each age group, we can assume that in 2009 died 44118 women in Portugal (note that we consider "women" as female gender individuals that have 20 years old or plus), 48,9% of them in the first semester of the year, and 51,1 % in the second semester. This means that the female mortality tax in Portugal, in 2009 was of 0,8% of global female population, showing a significant decreased, considering the tax previously calculated in 2005, of 0,16%.

However, reminding the previous age group reasoning and considering that BC caused 3,1% of global mortality in 2009, we can define age and time related mortality due to breast cancer, as presented in the tables bellow:

	1st Sem	2nd Sem	NBNRMR	1st Sem	2nd Sem	BCRMR
Age groups	**Deaths**	**Deaths**	**Deaths**	**BC Deaths**	**BC Deaths**	**Deaths**
25-64 years	2759	2879	5638	86	89	**175**
65-109 years	18832	19648	38480	584	609	**1193**
Total	21591	22527	44118	669	698	**1368**

Table n. 15: 2009 Annual Number of Female Non-Related to BC and BC Related Mortality Rates, According to Age Group and semester.
Source: Own calculations.

	1st Sem	2nd Sem	BCRMR
Age groups	BC Deaths %	BC Deaths %	**Deaths %**
25-64 years	0,19	0,20	**0,40**
≥ 65 years	1,32	1,38	**2,70**
Total	1,52	1,58	**3,10**

Table n. 16: 2009 Annual Percentage of Female BC Related Mortality Rate by Age Group and Semester, regarding the global number of female deaths that year.
Source: Own calculations.

We can thus conclude that **0,4% of female deaths will be BC related at the age range between 25-64 years old, and that 2,7% of female deaths will be caused by BC at the age range of more that 65years**. There is also a very little distinction between the first and second year semesters that will be not considered in the model, since this difference is not significant in the overall data.

2.3.2.2.5. TRANSITION PROBABILITIES

2.3.2.2.5.1. DISEASE SEVERITY

Cancer stages are based on the size of the tumor, whether the cancer is invasive or non-invasive, whether lymphatic nodes are involved, and whether the cancer has spread beyond the breast.
The purpose of the staging system is to help organizing the different factors and some of the personality features of the cancer into categories, in order to:

- best understand your prognosis (the most likely outcome of the disease);
- guide treatment decisions (together with other parts of pathology reports), since clinical studies of BC treatments to consider are partly organized by the staging system;
- provide a common way to describe the extent of BC for doctors and nurses all over the world, so that results of your treatment can be compared and understood;

The BC stage system presented (and described below) is commonly used in recent published BC studies, as in the one of Hosmer, Malin & Wong (2010), for example.

Stage 0 is used to describe non-invasive BCs. In stage 0, there is no evidence of cancer cells or non-cancerous abnormal cells breaking out of the part of the breast in which they started, or of getting through to or invading neighboring normal tissue.

Stage I describes invasive BC (cancer cells are breaking through to or invading neighboring normal tissue) in which:

- the tumor measures up to 2 centimeters, and
- no lymph nodes are involved

Stage II is divided into subcategories known as IIA and IIB.

Stage IIA describes invasive BC in which:

- no tumor can be found in the breast, but cancer cells are found in the axillary lymphatic nodes (under the arm), or
- the tumor measures 2 centimeters or less and has spread to the axillary lymphatic nodes, or
- the tumor is larger than 2 centimeters but not larger than 5 centimeters and has not spread to the axillary lymphatic nodes

Stage IIB describes invasive BC in which:

- the tumor is larger than 2 but no larger than 5 centimeters and has spread to the axillary lymphatic nodes, or
- the tumor is larger than 5 centimeters but has not spread to the axillary lymphtic nodes

Stage III is divided into subcategories known as IIIA, IIIB, and IIIC.

Stage IIIA describes invasive BC in which either:

- no tumor is found in the breast. Cancer is found in axillary lymphatic nodes that are clumped together or sticking to other structures, or cancer may have spread to lymphatic nodes near the breastbone, or
- the tumor is 5 centimeters or smaller and has spread to axillary lymphatic nodes that are clumped together or sticking to other structures, or
- the tumor is larger than 5 centimeters and has spread to axillary lymphatic nodes that are clumped together or sticking to other structures

Stage IIIB describes invasive BC in which:

- the tumor may be any size and has spread to the chest wall and/or skin of the breast; or
- may have spread to axillary lymphatic nodes that are clumped together or sticking to other structures, or cancer may have spread to lymphatic nodes near the breastbone;
- Inflammatory BC is considered at least stage IIIB.

Stage IIIC describes invasive BC in which:

- there may be no sign of cancer in the breast or, if there is a tumor, it may be any size and may have spread to the chest wall and/or the skin of the breast, and
- the cancer has spread to lymph nodes above or below the collarbone, and
- the cancer may have spread to axillary lymphatic nodes or to lymphatic nodes near the breastbone

Stage IV describes invasive BC in which:

- the cancer has spread to other organs of the body - usually the lungs, liver, bone, or brain.

"*Metastatic at presentation*" means that the BC has spread beyond the breast and nearby lymphatic nodes, even though this is the first diagnosis of breast cancer. The reason for this, is that the primary breast cancer was not found when it was only inside the breast. *Metastatic cancer* is considered to belong to stages III and IV.

Summarizing, in our model we will consider six levels of disease, corresponding to disease progression stages and death. To define early stage BC we will consider stages 0, I and II; and to define advanced/metastatic BC, stages III and IV (as mentioned).

In the study of Hosmer, Malin & Young (2010), BC stage incidence at diagnosis was evaluated and results showed that **21,8% were at stage I, 54,6% were at stage II, 16,1% were at stage III and 7,4% were at stage IV of the disease**.
At stage 0, we will consider the surplus to 100% (of only 0,1%).

These levels and incidence rates will be integrated in the data processor as forming the basic structure of the disease progression Markov stages, as we shall see latter.

2.3.2.2.5.2. FACING COMPLICATIONS

The toxicities associated with chemotherapeutic agents are usually classified as **immediate** (occurring during or immediately after treatment), **intercurrent** (occurring between courses of treatment) **or cumulative** (occurring after several courses of treatment) (Brown, Lipscomb & Snyder, 2001).

Immediate toxicities, such as nausea and vomiting, are assumed to discontinue after completion of each course of chemotherapy and therefore were not taken into account in the model.
Neutropenia and acute diarrhea are the most common intercurrent toxicities.
Cumulative toxicities that could be encountered with salvage chemotherapy and included in the model were **acute renal failure, cardiovascular toxicity, acute hepatic failure, acute pulmonary disease, arthralgia, and osteoporosis**.

We followed the study of Brown, Lipscomb & Snyder (2001) and **assumed that these conditions are severe and that persisted for 9 weeks, period where the patients are withdrawn from chemotherapy.**

Major disease and therapy adverse events with statistic significant differences in frequency of occurrence, were accounted for in the model.
The CHEUAL BC model is composed by **nine complication sub-models (SM), each of which simulate different complications associated with the disease and/or therapy adverse effects** (metastasis incidence (soft tissue, bone and visceral metastasis) (Karnon & Brown, 2002; Karnon *et al.*, 2006; Epstein *et al.*, 2006), acute renal failure (Palmer *et al*, 2004[a], Brown, Lipscomb & Snyder, 2001, Dranitsaris *et al.*, 2009), cardiovascular disease (thromboembolic events (Karnon & Brown, 2002; Epstein *et al.*, 2006), cerebrovascular ischemia (Dedes *et al.*, 2009), and acute myocardial infarction (Palmer *et al*, 2004[a]; Kurian, A *et al.*, 2007; Liberato, Marchetti & Barrosi, 2007)), severe arthralgia (Brown, Lipscomb & Snyder, 2001; Karnon *et al.*, 2006), acute hepatic failure (Wolfe, Ashby, Milford, Ojo, Ettenger, Agodoa, Held, & Port, 1999), acute pulmonary disease (Karnon & Brown, 2002), acute cytopenia (anemia (Dranitsaris *et*

al., 2009), thrombocytopenia (Dranitsaris *et al*., 2009), leucopenia (Brown, Lipscomb & Snyder, 2001; Dranitsaris *et al*., 2009) and febrile neutropenia leading to infection (Brown, Lipscomb & Snyder., 2001; Dranitsaris *et al*., 2009; Karnon & Brown, 2002)), osteoporosis (Karnon *et al*., 2006; Epstein *et al*., 2006) and acute diarrhea (Dranitsaris *et al*., 2009).

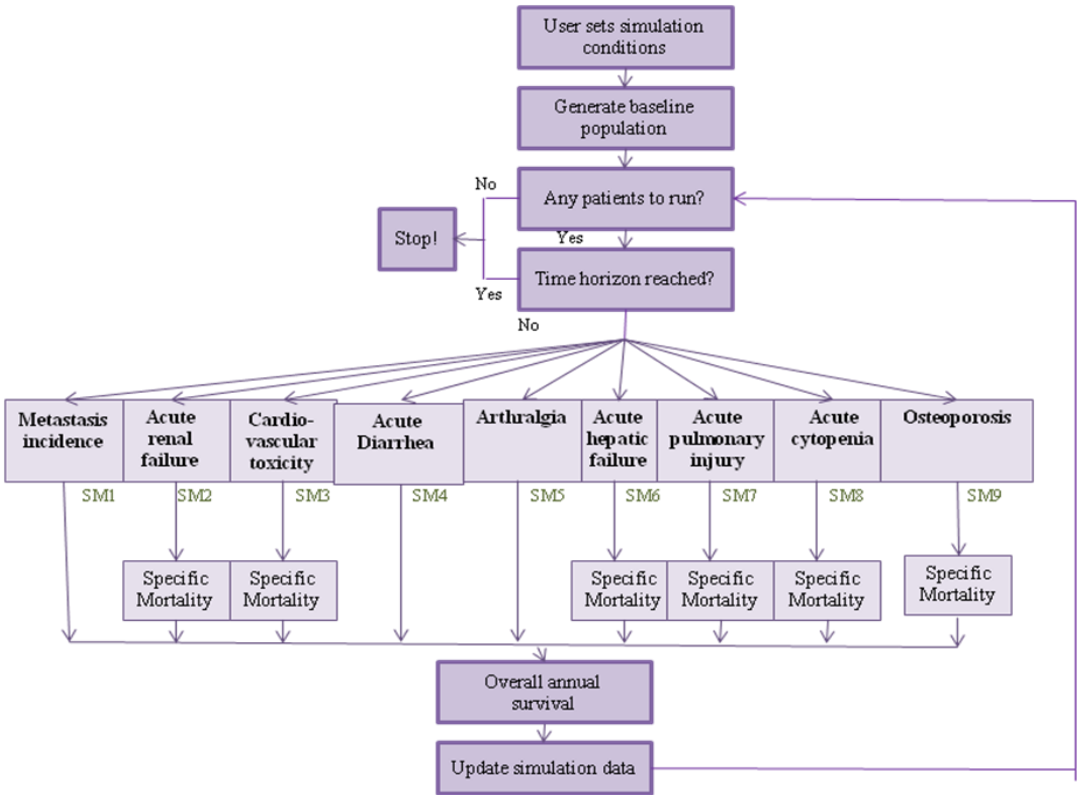

Figure n. 7: Scheme of the CHEUAL disease complication and therapy adverse effects sub-models.
Source: Addapted from Palmer *et al.* (2004)[a]

For example, a patient may have cancer, but also heart disease and anemia so severe that the costs and risks of the treatment outweigh the short term benefit from treatment of cancer (Charlson, Pompei, Ales & MacKenzie, 1987).

Consider a patient who has a cardiac disease history and that is receiving cardio-toxic chemotherapy. Such a patient is more likely to suffer an embolic or hemorrhagic event than other patient with no cardiovascular disease history, highly increasing morbidity (short-term and/ or chronic), disease stage transition probability to the next level or even patient's death. The same reasoning can be applied to each SM.

Each SM is though implemented to capture the long-term progressive nature of BC, simulating the progress of patients through different disease stages due to disease and/or therapy complications (Palmer *et al*, 2004[a]).

Note that main pre-medication is used to prevent/minimize chemotherapy related adverse effects/complications, although not taken in account in this study, as previously described.

To estimate the global complication incidence, we have two choices:

- Using the follow-up study of BC patients of Paskett, Herndon, Day, Stark, Winer, Grubbs, Pavy, Shapiro, List, Hensley, Naughton, Kornblith, Habin, Fleming, & Bittoni (2008), that showed that there is a 2,32 odds ratio (OR) of one co-morbidity and a 2,93 OR of having two or more co-morbidities after an average of 13 years post-diagnosis. The co-morbidities included were: other cancers or leukemia, arthritis, rheumatism or other connective tissue disorder, glaucoma, emphysema or chronic bronchitis, high blood pressure, heart disease, circulation problems in legs/arms, diabetes, stomach or intestinal disorders, osteoporosis, chronic liver or kidney disease, stroke and depression.
- Or to use the data of total number of comorbid conditions in breast cancer at the time of the diagnosis (prior to treatment), in 65 and more years age group, taken from the study of Hosmer, Malin & Wong (2010), like next presented.

Number of comorbid conditions	%
0	49,2
1	27,7
2 or more	23,1

Table n.17: Probability of developing complications after BC diagnosis.
Source: Own calculations based on data presented in the study of Hosmer, Malin & Wong (2010).

Evaluating the two options presented, the study of Paskett *et al.* (2008) considered co-morbidity diseases that we hadn´t contemplated as complication SMs in our study, although the ones with the highest weight were. However, it shows the OR of co-

morbidities after an average of 13 years post-diagnosis, when we intend to consider 10 years the pos-surgery/RT phase.

On the other hand, the second study of Hosmer, Malin & Wong (2010) relates to the age range of 65 and older, while in our model we assume this and other first age interval, between 24-64 years old. But, as this data has probabilities of developing complications per disease stage at diagnosis, we decided to despise the age range limitation and adopt it into our study, although acknowledging the error associated. Also note that, in order to simplify complication odds calculations, and considering that the number of co-morbid conditions need to be the smallest possible for cytostatic therapy administration, we decided to consider the incidence of 23,1% for two complications, despised the odds of three or more.

2.3.2.2.5.2.1. METASTASIS INCIDENCE

Block *et al*. (2009), studied whether the effects of prognostic factors associated with the occurrence of distant metastases at primary diagnosis changed after the incidence of *loco-regional recurrences (LRR)* among women treated for BC, stages I or II, measured in *adjusted hazard ratios (HR)*, with 95% confidence intervals, at a significance level of 0.05. It was assumed that stage-dependent covariation was zero before the incidence of a LRR, and that became one, after the incidence of a LRR.

They concluded that the presence of a **LRR** in itself is a significant prognostic risk factor (**3.64**HR) for the occurrence of *distant metastasis (DM)*, as presented in the table below.

Characteristics	Transition 1: from surgery to LRR (8,6%)	Transition 2: from surgery to DM (40.0%)	Transition 3: from LRR to DM (3.6%)
Age at diagnosis			
≥50	1	1	1
40–50	1.42 (1.09–1.85)	0.95 (0.81–1.11)	0.94 (0.62–1.41)
≤40	1.79 (1.28–2.51)	1.45 (1.19–1.76)	0.85 (0.51–1.42)
Tumor size			
<2 cm	1	1	1

2–5 cm	1.07 (0.83–1.37)	1.58 (1.35–1.84)	1.12 (0.74–1.69)
Nodal state			
Node-negative	1	1	1
Node-positive	1.17 (0.89–1.55)	2.00 (1.74–2.30)	1.69 (0.13–2.53)
Surgical therapy			
Mastectomy	1	1	1
Breast-conserving surgery	2.26 (1.63–3.12)	0.93 (0.81–1.07)	1.22 (0.70–2.11)
Perioperative chemotherapy			
No	1	1	1
Yes	0.68 (0.52–0.90)	0.95 (0.82–1.09)	1.20 (0.81–1.77)
Adjuvant chemotherapy			
No	1	1	1
Yes	0.82 (0.57–1.19)	0.66 (0.55–0.80)	1.35 (0.83–2.21)
Adjuvant radiotherapy			
No	1	1	1
Yes	0.59 (0.41–0.84)	1.05 (0.88–1.25)	1.27 (0.70–2.32)
Loco-regional recurrence present			3.64 (2.02–6.55)

Table n.18: Characteristics of all patients with respect to parameter estimates related to each transition.
Source: Block *et al*. (2009).

In our study we assumed the incidence of LRR or the occurrence of DM as *metastasis incidence*. We didn´t made any distinction between them, so we decided to recognize the worse scenario, considering the average of both, as it is shown bellow.

Characteristics	HR LRR	HR DM	HR LRR + HR DM
Age at diagnosis			
>65	1	1	**2**
24-65	1,40	1,13	**2,54**
>50	1	1	2
40–50	1,42	0,95	2,37
≤40	1,79	1,45	3,24
Tumor size			
<2 cm	1	1	**2**
2–5 cm	1,07	1,58	**2,65**
> 5cm	1,14	2,16	**3,3**
Nodal state			

Node-positive	1,17	2	**3,17**
Surgical therapy			
Mastectomy	1	1	2
Breast-conserving surgery	2,26	0,93	3,19
Surgery	1,63	0,97	**2,60**
Adjuvant chemotherapy			
Yes	0,82	0,66	**1,48**
Adjuvant radiotherapy			
Yes	0,59	1,05	**1,64**

Table n.19: Characteristics of all patients with influence in disease metastasis incidence.
Source: Adapted from Block *et al*. (2009) and adding own calculations.

Looking closely to the results presented, attending to the age at diagnosis and tumor size grouping previously considered, we tried to calculate the pieces missing. To calculate the metastasis incidence HR for age interval >65, we adopted the value presented in the study of Block *et al.* HRs of >50 age group; the other age group value is product of the average of HRs considered in the same study that, in our opinion, are maladjusted reminding the BC incidence and prevalence values at each age interval at diagnosis. Likewise, the HR associated with tumors bigger than 5cm were also despised in the study of Block *et al.* (2009), as it only considers stages I and II (is an early BC study) so, to evaluate it, we assumed that the increasing HR varied in the same proportion presented from smaller size tumor intervals.
On the other hand, as previously quoted, perioperative chemotherapy (systemic chemotherapy administered within a few days following surgery) is not a standard treatment for BC, being despised in our study.

After the metastasis incidence summary table analysis, we assume that the main prognostic risk factors for metastasis incidence are **young age** at diagnosis **(HR 24-64 years** = **2,54**; HR **≥ 65 years = 2**), large **tumor size (HR >5cm = 3,3; HR 2-5 cm = 2,65; HR <2cm = 2**) and **lymphatic node positivity (HR + =3,17; HR - = 2).**
On the other hand, **adjuvant chemotherapy, surgery and radiotherapy have a protective effect of 2,60, 1,48 and 1,64 HRs, respectively**, wich means that this benefit must be considered in the progressive disease state (Block *et al*., 2009).

Considering all of this factors, we had calculated the global metastasis incidence HR for each disease stage and age group at diagnosis. The results are presented in the table below.

Stage	Tumor size	Lymphatic node Positivity	Metastasis incidence HR : 24-64years	Metastasis incidence HR : ≥ 65 years
0	-	-	0	0
I	< 2cm	-	0	0
IIA	< 2cm	+	9,79	6,37
	2-5cm	-	0,42	0
IIB	2-5cm	+	15,03	10,49
	> 5cm	-	2,07	0,29
IIIA	-	++	1,74	0,03
	≤ 5cm	++	15,03	10,49
	> 5cm	++	20,26	14,61
IIIB, IIIC, IV	Metastisation to other structures/ organs		20,26	14,61

Table n.20: Disease metastasis incidence percentage according to disease stage and age group at diagnosis.

Source: Own calculations.

We think that there was no point associating metastasis incidence with mortality, since metastasis are directly associated with disease progression stages and with organ destruction, those possibly related with mortality rates. Metastisation is therefore not directly related to fatal events. This idea is shared by Palmer *et al.* (2004)[a].

2.3.2.2.5.2.2. ACUTE RENAL FAILURE/ NEPHROPATHY

In the study of Diel, Weide, Köppler, Antras, Smith, Green, Wintfeld, Neary, & Duh (2009), in BC patients doing chemotherapy (56% of patients), the renal function was assessed by the measurement of *serum creatinine (SCr)* and *glomerular filtration rate (GFR).*

Patients were defined as experiencing renal impairment based on two different definitions:

(1) SCr-based definition: if they had an increase in SCr of ≥0,5 mg/dL (if baseline <1,4 mg/dL) or 1,0 mg/dL (if baseline ≥1,4 mg/dL);

(2) GFR-based definition: a ≥25% increase in GFR from baseline.

Note that 4,7% of patients doing Zoledronic Acid and 11,0% of those doing Ibandronate had already had a history of renal disease (Diel *et al*., 2009). Hosmer, Malin & Wong (2010) showed that **1,3 % of elderly BC patients (≥ 65 years) had already developed chronic renal disease before initiating chemotherapy**, which suggests that the results of the first study may be overvalued. However, according to the *Portuguese Society of Nephrology* is estimated that more than 800 000 people suffer from the disease. Each year are registered 2.200 new cases of terminal chronic renal failure and there are currently 15.000 patients with this condition (10.000 dialysis-dependent and 5.000 transplanted).

Regarding the resident population number, 10 637 713, we can extrapolate that **7,5% of patients present a previous history of renal disease**, result very close to the average between the values given for different molecules in the first study (Diel *et al.*, 2009).

The renal impairment incidence rate (number of events per patient per year of treatment with bisphosphonates) was significantly higher in the Zoledronic acid group than in the Ibandronate group, whether assessed by SCr (0,56 versus 0,21, p<0.0001) or by GFR (1,92 versus 1,01, p<0.0001). However, as experienced in the described study, **renal impairment relative risk of SCr is of 1,5,** although GFR relative risk is of 1,3. So, we decided to account the renal impairment based on SCr, with a higher relative risk, and to assume the average value of the substances described (not forgetting that they´re different from the ones used in our study, not even belonging to the same pharmaceutical category).

Wolfe *et al.* (1999) defined different cancer disease stages based on renal disease status (*No renal complications*, *Micro-albuminuria*, *Gross-proteinuria*, *ESRD* (either *Haemodialysis*, *Peritoneal dialysis* or *Kidney transplant*) and *Death following ESRD*). In their model, microalbuminuria is defined as urinary excretion of 30-300mg of albumin per 24hours and gross proteinuria is an excretion greater than 300mg of albumin per 24 hours. The probability of progression from one stage to another is dependent on BC treatment patterns and ethnic group. However, Wolfe´s study model

incorporate variables very different from the ones used in the CHEUAL model, reason why they were not considered.

In the study of Liano & Pascual (1996), 748 patients (age range from 15 to 95 years; mean 64 years; 65% male) with acute renal failure (either on admission or developed during hospital stay) from 13 Spanish tertiary care hospitals were followed until discharge during a period of 30 days. From those, 337 died during this period, indicating **that acute renal failure is associated with a mortality rate of around 45%.**

2.3.2.2.5.2.3. CARDIO-VASCULAR DISEASE

Palmer *et al* (2004[a]) adopted a *myocardial infarction (MI)* sub-model to integrate the cardiac disease history in the CORE Diabetes Model. This SM was composed of three stages: *No history of MI*, *History of MI* and *Death following MI*. This model uses the **Framingham risk function** to calculate probabilities of MI, based on a proportional hazard regression model published by D'Agostino, Russell, Huse, Ellison, Silbershatz, Wilson, Hartz (2000). The regression model predicts the probability of the first MI. The risk of recurrent MI is indexed by year after the first MI and is based on data from Sweden, published by Herlitz, Bang & Karlson, in 1996. The probability of death following MI is dependent on the time after the event and is taken from several published sources based on the study of Sonke, Beaglehole, Stewart, Jackson, & Stewart (1996). Risk adjustments to the SM can be made for the association with the onset of renal disease or any previous markers of increased risk of cardiovascular disease.

In the study of Paskett *et al.* (2008), *The Survivor's Health and Reaction Study*, used a quality-of-life model adapted **for cancer survivors, who were 9,4–16,5 years post-diagnosis completed**, to identify factors related to global HR-QOL and to document the prevalence of problems and health-oriented behaviors in a follow-up study of BC patients who participated in the CALGB 8541 study. The model revealed mainly **heart disease with a OR of 5,01**, with a 95% Cl.

Like heart insufficiency, *venous thromboembolism (VTE)* is a common and life-threatening complication in patients with cancer. Chemotherapy has been identified as a risk factor for this disease. The study of Agnelli and Verso (2007) shows that the annual incidence of VTE in cancer patients receiving chemotherapy is estimated to be about 10%. This risk increases up to 15-20%, depending on the type and combination of anticancer drugs. Hormonal and supportive therapies are also associated with increased risk for thromboembolic complications. Furthermore, emerging data supports the hypothesis of the occurrence of VTE events in cancer patients being associated with a poor prognosis.

The most accurate assessment on the rate of VTE during chemotherapy derives from studies in women with BC. From the results of these studies can be summarized that the **risk of VTE in patients with early stage BC, in absence of anticancer therapy, is slightly increased (0,5% approximatel**y), in comparison with the general population rate. This risk of VTE increases to 10% when adjuvant chemotherapy is used and **in case of combined use of chemo and hormonal therapy, this risk rises to 15%.** For patients with **metastatic stages, these rates were as high as 18%, in the presence of combined treatments.**

The study of Hosmer, Malin & Wong (2010) showed that **12,6% of the elderly BC patients (≥ 65 years) had already developed cardiovascular disease before initiating chemotherapy, 5,9% of which had congestive heart failure and 6,7% revealed peripheral vascular disease.**

The *EPICA (Epidemiology of Heart Failure and Learning)* Study (2004) showed that the **incidence of chronic heart failure is 4.36% for the Portuguese population with more than 25 years**, which means that about 260.000 patients of this age group suffer from cardiac insufficiency.

If we assume that the incidence between chronic heart failure and peripheral vascular disease for our country is at the same proportion found in the study of Hosmer, Malin & Wong (2010), we can conclude that, **in Portugal, there is a chronic venous insufficiency incidence of 4,95%** in women above 24 years.

The global cardiovascular disease incidence in the country will therefore be of 9,31%.

Data from the *Portuguese Society of Cardiology* from 2009, and supported by the study of Araújo *et al.* (2009), told us that **cardiovascular disease is** the leading cause of death in Portugal, being **responsible for around 40% of deaths in the country**.

2.3.2.2.5.2.4. ARTHRALGIA/JOINT PAIN

For Mao (2009), arthralgia is common in postmenopausal BC survivors who are receiving AIs. In this study, 57,7% of patients that developed acute arthralgia events were taking anastrozole, 23% were taking letrozole, and 19% were taking exemestane. In this cross-sectional survey of postmenopausal BC survivors, who were receiving adjuvant AI therapy, 47% of patients reported attribution of AIs as a cause of their current joint pain. Of those patients, 74% recognized the onset within 3 months after starting medication. However, 30,3% of patients attributed joint symptoms to previous osteoarthritis, 32,3% attributed joint symptoms to other medical conditions (fibromyalgia, rheumatoid arthritis, spinal stenosis), 4.3% attributed joint symptoms to other medications (statin, paclitaxel), and 21% to other causes (mainly ‘‘aging,’’ injury).
The most common sites of joint pain in individuals who had AI-related arthralgia were wrist/hand (60.4%), knee (59.7%), back (54%), ankle/foot (51.8%), and hip (42.5%), in descending order.
As we haven´t found other published source of the impact of BC medicines in rheumatologic diseases, we will consider the presented percentage of patients with joint pain after chemotherapy and extrapolate it to all BC therapy cycle, indicating that we will assume that **47% of BC patients will suffer from arthralgia related to chemo, hormonal and immunotherapy.**

On the other hand, Hosmer, Malin & Wong (2010) showed that **3,2% of elderly BC patients (≥ 65 years) had already developed rheumatologic disease before initiating chemotherapy**.

According to data from the *Portuguese Institute of Rheumatology*, there are about 1.000.000 Portuguese rheumatologic patients (around 10% of population). However, we don´t have specific data of how many of these patients suffer from severe arthralgia. It was for this reason that we opt to adopt the value presented by Hosmer, Malin & Wong (2010).

Although associated with high morbidity, our opinion, supported by the study of Palmer *et al.* (2004), is that arthralgia is not directly associated with death events.

2.3.2.2.5.2.5. ACUTE HEPATIC FAILURE

According to the *Portuguese Society of Hepatology*, it is estimated that there is about 1,5 million people suffering from some liver disease in Portugal. Regarding the resident population number, 10 637 713, that means that 14,1% of the population would suffer from any kind of liver disease prior to BC/chemotherapy.

This result is very different from the one presented by Hosmer, Malin & Wong (2010), which indicates that 0,4% of BC elderly patients have history of liver disease.

According to the study of Bilici, Ozguroglu, Mihmanli, Turna, Adaletli, & Serdengecti (2003), patients with BC sometimes present increased liver enzymes during a follow-up period, that may be consistent with hepatic steatosis, effect known as non-alcoholic fatty liver disease (NAFLD). They studied the influences of primary disease and treatment on steatosis in patients with BC:

1) newly diagnosed, previously untreated BC;
2) BC treated with systemic therapy; and
3) healthy women.

They detected steatosis in 63%, 72%, and 48% of patients in groups 1, 2 and 3, respectively.

This indicates that steatosis is more frequent in BC patients than in healthy women, and that BC treatment induces liver toxicity.

However, NAFLD in patients with BC may be associated with some well known risk factors such as obesity, hyperlipidemia and diabetes mellitus, explaining the huge difference between this and other studies data of liver disease in non-cancerous population.

Trying to adapt the described data to our model, we decided to consider the **national incidence of liver disease (14,1%)** and to keep the proportion of data of BC patients found in the study of Bilici *et al.* (2003), **namely for liver disease incidence in BC newly diagnosed untreated patients (18,5%) and in BC patients treated with systemic therapy (21,2%).**

Liver steatosis is associated with increased mortality from cardiovascular disease, and cancer, even after adjustment for other potentially confounding coexisting disorders such as obesity and type 2 diabetes mellitus. A study from the US (Olmsted County, Minnesota), revealed that **patients with NAFLD died 10% more versus control subjects, over a 10-year period**. Malignancy and heart disease were the top two causes of death. **Liver-related disease was the third cause of death (13%),** as compared to the 13th cause of death (<1%) for control subjects (Kotronen, A; Peltonen, M.; Hakkarainen, A.; Sevastianova, K.; Bergholm, R.; Johansson, L.; Lundbom, N.; Rissanen, A.; Ridderstrale, M.; Groop, L.; Orho-Melander, M. & Yki-Järvinen, H., 2009).

2.3.2.2.5.2.6. ACUTE PULMONARY DISEASE

The study of Lind, Wennberg, Gagliardi, & Fornander (2001), investigates the incidence of short-term pulmonary complications following *radiotherapy (RT)* for BC.
Moderate pulmonary complications, that require treatment with corticosteroids, were rare following local RT (<1%), but were diagnosed among 11% of the patients treated with loco-regional RT. Among the subgroup of mastectomised patients treated with LR-RT, a difference in mean pulmonary injury values was found within patients experiencing both clinical and radiological pulmonary side-effects as it is summaryd in the table below.

Factor	Complications[a] (*n*=62)	*P*-value
Lung disease	**7/62(11%)**	0.12[c]
Chemotherapy	24/62(39%)	0.02[c]
Hormonal Therapy	35/62(56%)	0.03[c]
Reduced function	27/60(45%)	0.003[c]

aMild and moderate.
cChi-square test.

Table 21. Univariate analysis for the effect of potential confounding factors on the development of pulmonary complications following loco-regional RT after mastectomy.
Source: Adapted from Lind *et al.* (2001).

As we will evaluate the treatment effects after surgery (mastectomy) following loco-regional radiotherapy (if adequate, as previously referred), this data is of extreme importance to define pulmonary complication odds before and after systemic therapy. We may conclude that **before initiating the chemotherapy cycles 11% of BC patients (previously submitted to surgery and RT) developed pulmonary injury complications**; that after chemotherapy cycles, these patients have 39% probability of developing these complications; and that after hormonal therapy cycles, 56% of patients will suffer from pulmonary complications.

Unfortunately, and because this is a study from 2001, immunotherapy wasn´t still current and wasn´t thought evaluated. However, we decided to contemplate de same value of pulmonary injury reveled to hormonal therapy for immunotherapy, since trastuzumab reveled pulmonary side effects as previously shown. On the other hand, there wasn´t found any recent studies of pulmonary complications in BC patients.

Note that, if chemotherapy isn´t working, patients may start other second line BC chemotherapy cycle and leave hormonal/immunotherapy as soon as possible. This turns difficult to calculate different treatment pulmonary injury odds, keeping in mind the differences within a six-month follow-up cycle (as we shall consider). For this reason, we decided to take into account the **average value of pulmonary injury odds after therapy**, regardless the type of active substances being administrated, and recalling the value for the therapy most currently used protocol, **of 47,5%.**

Data from the study of Hosmer, Malin & Karlson (2010) indicates that 13,8% of BC elderly patients have previous history of *chronic pulmonary disease (CPD)* at the time of the disease diagnostic.

According to the *Portuguese Society of Pneumology* **5,42% of the Portuguese population is estimated to suffer from *Chronic Obstructive Pulmonary Disease (COPD)***, between 35 and 69 years. COPD is a pulmonary disease that results from an airway obstruction. Under this designation are included both chronic bronchitis and pulmonary emphysema.

As we haven´t find any more data available, we decided to consider the data from COPD incidence in Portugal (of 5,42%) for the history of disease item of the two age groups chosen to the CHEUAL BC model. We chose to consider COPD in detriment of the history of CPD regarded by Hosmer, Malin & Wong (2010), because of the higher severeness degree of the first, more directly related with pulmonary complication odds.

A prospective study from Gudmundsson, G.; Gislason, T.; Lindberg, E.; Hallin, R.; Ulrik, C.; Brøndum, E.; Nieminen, M.; Aine, T.; Bakke, P & Christer Janson (2006), which included 416 COPD patients, from five Nordic countries, used the *St. George's Respiratory Questionnaire (SGRQ)* to obtain information on treatment and co-morbidity. Patients were followed for 24 months. During the follow-up period 122 (29,3%) of the 416 patients died. The primary cause of death was respiratory in 79 patients, cardiovascular in 21, malignancy in 7, and *other causes* in 3 patients, whilst no information on causes of death was available for 12 patients. This means that **mortality directly due to COPD (respiratory reasons) is of around 19%.**

2.3.2.2.5.2.7. ACUTE CYTOPENIA

Cytopenia is a reduction in the number of blood cells. It takes a number of forms:

- Low red blood cells count: resulting in **anemia**;
- Low white blood cells count: leukopenia or **neutropenia** (because neutrophils make up at least half of all white cells, they are almost always low in leukopenia);
- Low platelets count: **thrombocytopenia**;
- Low granulocytes count: granulocytopenia;

- Low red blood cells, white blood cells and platelets count: pancytopenia;

According to the *European Cancer Anemia Survey (ECAS)*, anemia associated with cancer decreases the of quality of life of patients and may affect the outcome of cancer treatment. One of the main symptoms of anemia in patients with cancer is fatigue. The study conducted by Curt, Breitbart, Cella, Groopman, Horning, Itri, Johnson, Miaskowski, Scherr, Portenoy, & Vogelzangk (2000), met a sample of 379 cancer patients, and 76% of them were reported having fatigue during chemotherapy. Of these, 30% confirmed suffering from fatigue daily. Their research proves that fatigue makes it difficult to participate in social activities and that has implications in the reduction of cognitive abilities. Of 177 patients who were employed, 75% changed their terms of employment due to fatigue.

Activities such as travel distances (69%), cleaning the house (69%), exercise (67%) and social activities with friends and family (59%) require a degree of effort too huge for cancer patients presenting this symptom.

According to the ECAS study, which took place in 748 cancer care centers, in 24 European countries, with 1,000 doctors and 15,367 patients enrolled, approximately **67% of European patients with cancer suffered from anemia**.

The study of Kirshner, Hatch, Hennessy, Fridman, & Tannous (2004) investigated the medical charts of 310 BC patients who received adjuvant chemotherapy with doxorubicin and cyclophosphamide. Prechemotherapy anemia was defined as a baseline hemoglobin of < 12g/dl. An anemic event during chemotherapy was defined as either a drop in hemoglobin level below the threshold (≤ 10g/dl), the receipt of a blood transfusion or treatment with epoetin alpha. Results showed that **31,3% of patients were anemic prechemotherapy, 61,9% of which developed moderate to severe anemia during chemotherapy. On the other hand, 41,8% of patients with normal prechemotherapy hemoglobin levels experienced moderate to severe anemic events.**

In the study of Izaks, Westendorp, & Knook (1999), a total of 755 hemoglobin concentrations were measured in persons aged 85 years and older. The 5-year mortality rate of these individuals increased almost twofold in the presence of anemia, and anemia was proven to be an independent risk factor for death. The risk of mortality increased

with the degree of **anemia**. Note that compared with persons with a normal hemoglobin concentration, **the mortality risk was 1,60 higher in women with anemia**.

Neutropenia is a condition in which the number of neutrophils or white blood cells in the bloodstream is decreased. An *absolute neutrophils count (ANC)* of less than 1500 per blood micro liter (1500/microL) is the generally accepted definition of neutropenia. Neutropenia is sometimes further classified as:

- mild, if the ANC ranges from 1000-1500/microL,
- moderate, with an ANC of 500-1000/microL, and
- severe, if the ANC is below 500/microL.

Neutrophils are also known as polymorph nuclear leukocytes. Neutropenia affects the body's ability to fight off infections, which means that patients are at greater risk of succumbing to infection that may culminate in sepsis and in an increased risk of mortality. Patients who develop severe **neutropenia with fever**, indicating added risk of infection, may be withdrawn from chemotherapy (Brown, Lipscomb & Snyder, 2001).

In our study, we will mainly consider febrile neutropenia, considering its severeness degree, direct relation to systemic chemotherapy substances and ability to increase morbidity.

In the study of Hosmer, Malin & Wong (2010) was analyzed the SEER-Medicare data (1994–2005) to develop and validate a prediction model for hospitalization with fever, infection or neutropenia occurring after chemotherapy initiation for patients with BC. Febrile neutropenia is the major dose-limiting toxicity of systemic chemotherapy, being associated with delays in treatment, hospitalization, higher costs, and mortality ranging from 4% to 21%. In that study, **BC patients reveled a febrile neutropenia percentage of 4,1% after the first cycle of chemotherapy.** Note that this same study revealed an hematologic disorder of 15,4%.

According to the assessment conducted by Soong, Haj, and Leung (2009) from the Carlo Fidani Peel Regional Cancer Centre, the first 12 patients treated with an average dose of docetaxel and cyclophosphamide, of 73 mg/m^2 and 590 mg/m^2 respectively, infused over the first chemotherapy cycle, without growth factor prophylaxis, reported a 50% incidence (6 of 12 patients) of febrile neutropenia. Note that at baseline, all

patients had normal laboratory values and no active infection nor previous chemotherapy or radiation therapy. However, due to the small number of patients in the sample, this study data was not considered.

According to Kuderer, Dale, Crawford, Cosler, & Lyman (2006), hospitalization for febrile neutropenia in cancer patients is associated with considerable morbidity and mortality. They studied the medical chart of all adult cancer patients hospitalized with febrile neutropenia, from 115 US medical centers, between 1995 and 2000, comprising a total of 41.779 patients. Primary outcome included mortality rate. Results showed that overall, in-hospital mortality was 9,5%. Patients without any major co-morbidities had a 2,6% risk of mortality, whereas one major co-morbidity was associated with a 10,3% risk and more than one major co-morbidity, with a risk of mortality ≥ 21,4%.
However, to turn easier the calculations, we decided to consider only the **overall mortality, associated with febrile neutropenia, of 9,5%**, like previously described.

According to the study of Demers, Ho-Tin-Noé, Schatzberg, Yang & Wagner, (2011), thrombocytopenia generally occurs only in advanced metastatic breast cancer. Platelets contribute to homeostasis of the tumor vasculature by helping to prevent hemorrhage. Thus, these authors hypothesized that inducing thrombocytopenia in tumors would increase vascular leakness and facilitate the effective delivery of chemotherapeutic agents to tumors, suggesting that thrombocytopenia has a protecting effect, adding to fight the disease, although associated as a chemo-endocrine-immunotherapy complication.
However, this fact needs further investigation, since it has been reported in mice recently for the first time and not in humans.

In the study of Vogel, C.; Silverman, M.; Mansell, P.; Miller, A.; Thompson, J.; Herbick, J; Brunskill, B.; Padgett, D.; McKinney, E. & Sugarbaker, E. (2006), 13% of women treated with combination chemotherapy plus levamisole adjuvant immunotherapy, after mastectomy for BC stages II or III, developed levamisole-induced granulocytopenia. This complication occurred in each women between six and ten weeks after the completion of six months of chemo-immunotherapy, when they were taking levamisole alone. Granulocytopenia is a marked decrease in the number of

granulocytes. Granulocytes are a type of white blood cells filled with microscopic granules (little sacs containing enzymes that digest microorganisms). Neutrophils, eosinophils and basophils are all types of granulocytes. They are named by the staining features of their granules in the laboratory: neutrophils have "neutral" subtle granules; eosinophils have prominent granules that stain readily with the acid dye eosin; and basophils have prominent granules that stain readily basic (non acidic) dyes. This condition reduces the body's resistance to many infections.
Once we don´t contemplate the use of levamisole as adjuvant immunotherapy in the CHEUAL model (its use is not current in Portuguese hospitals) and because we had already considered the most severe complication associated with neutrophils (febrile neutropenia), we decided to ignore granulocytopenia in model development.

Unfortunately, we didn´t found any epidemiologic data of cytopenia disorders incidence in the country, leaving us the choice to consider that there was no previous history of disease for any of the conditions described in prechemotherapy phase. The association between thrombocytopenia and granulocytopenia was also despised.

2.3.2.2.5.2.8. OSTEOPOROSIS

According to information from the General Directorate of Health (2008), osteoporosis is a systemic skeletal disease, characterized by bone mass decrease and change of the quality of bone microstructure, leading to a decrease in bone strength and consequent increased risk of fractures, which were more frequent in dorsal and lumbar vertebrae, the distal radius and proximal femur. Proximal femur fractures are characterized, in the short term, by increased morbidity, mortality and high social and economic burdens.
Osteoporosis is a disease of high prevalence in Western countries, in which Portugal is inserted. According to data presented by the *Portuguese Society of Rheumatology* (2007), there are, **in our country, more than half a million people (around 5% of population), mostly women, with osteoporosis (in prechemotherapy phase)**.

The results of available clinical studies suggest that BC treatment significantly affect bone turnover, *bone mineral density (BMD)* and fracture risk. This is, for instance, the case for all third-generation AIs.

Most experts recommend that all women, starting medical castration or therapy with AIs, should be assessed for their risk of osteoporosis and undergo BMD measurement by dual-energy X-ray absorptiometry.

Patients with pre-existing osteopenia and osteoporosis should be evaluated for conditions that worsen skeletal health, such as vitamin D deficiency, hyperparathyroidism, hyperthyroidism and hypercalcuria. If these patients have a BMD score of −2.5 or lower, a low BMD (T-score between −1 and −2.5) and additional risk factors for osteoporosis or fragility fractures, biphosphonate therapy should be considered.

Most of the fracture evidence comes therefore, from tamoxifen-controlled studies, as it is shown in Rozenberg, Carly, Liebens & Antoine (2009). In this study, after a few years of AI use, women had a **20–35% increased fracture risk.**

Reinforcing these results, Paskett *et al*. (2008) presented a study of BC long-term survivors' quality of life and showed that **25% of patients had developed osteoporosis after therapy completion**. Similarly, Kanis, McCloskey, Powles, Paterson, Ashley & Spector (1999) found a 5-fold higher prevalence of vertebral fractures in BC patients than in women of the same age (OR of 4,7). They also found that osteoporosis is associated with mortality: **hip or vertebral fractures are associated with a 20% increase in mortality rate after 5 years**.

2.3.2.2.5.2.9. ACUTE DIARRHEA

From the study of Koroleva (2010), a retrospective multicenter case-control study on neoadjuvant and adjuvant chemotherapy for BC, was revealed that **13,6% of patients with acute inflammation** and destructive changes in the mucous membrane of the **colon, due to diarrhea, were related to an adverse effect of cytostatics in the course of chemotherapy.** It was also revealed a **higher incidence of toxicity in patients with a previous history of functional pathology of the intestine, which reached 22,7%.** In these patients, the trigger mechanism of toxicity was in the beginning of chemotherapy.

There was no increase in cumulative dose. However, it was noted a direct correlation between the severity of diarrhea and the severity of colitis.

In 2009, the *Study Group of the Portuguese Association of Inflammatory Bowel Disease* found that there were about 12.500 Portuguese patients with inflammatory bowel disease, which includes: Crohn's disease (about 6.000 patients) and ulcerative colitis (about 6,500 patients). Both diseases are characterized by chronic inflammation of unknown cause, that primarily affect the small intestine (in the case of Crohn's disease) or colon and rectum (in ulcerative colitis).
Regarding the resident population number, of 10.637.713 people, **0,12% of the population suffer from inflammatory bowel disease prior to BC/chemotherapy.**
As the number of patients with intestine pathologies is very little within the total number of BC patients, this incidence rate will be despised for model construction purpose.

In the *European Collaborative Study on Inflammatory Bowel Disease* cohort of Witte, Shivananda, Lennard-Jones, Beltrami, Politi, Bonanomi, Tsianos, Mouzas, Schulz, Monteiro, Clofent, Odes, Limonard, Stockbrügger, & Russel (2000), investigators filled out a standard follow-up form containing questions on the method of follow-up, vital status of the patient, change in diagnosis, extra-intestinal manifestations, medical and surgical treatment, and physician's global assessment of disease activity of a sample of 796 patients. The study results demonstrated that during the 4-year follow-up period, 23 patients died. The mean age at death was 69.3 years, but only the deaths of three patients were recorded as directly due to inflammatory bowel disease, representing a percentage of 0,38%.
Regarding this data, we chose not to consider an association between acute diarrhea and death.

2.3.2.2.5.3. INTEGRATING PROBABILITIES

2.3.2.2.5.3.1. DECISION TREE

The **decision tree** (figure n.8) can be called a "BC severity stage decision tree" and it represents the prognosis for a BC patient subsequent to the choice of a therapy management strategy, as previously used by Karnon & Jones (2003). The first chance node, labeled **antineoplasic systemic therapy option** has six branches, labeled **stage 0, stage I, stage II, stage III, stage IV and death.**

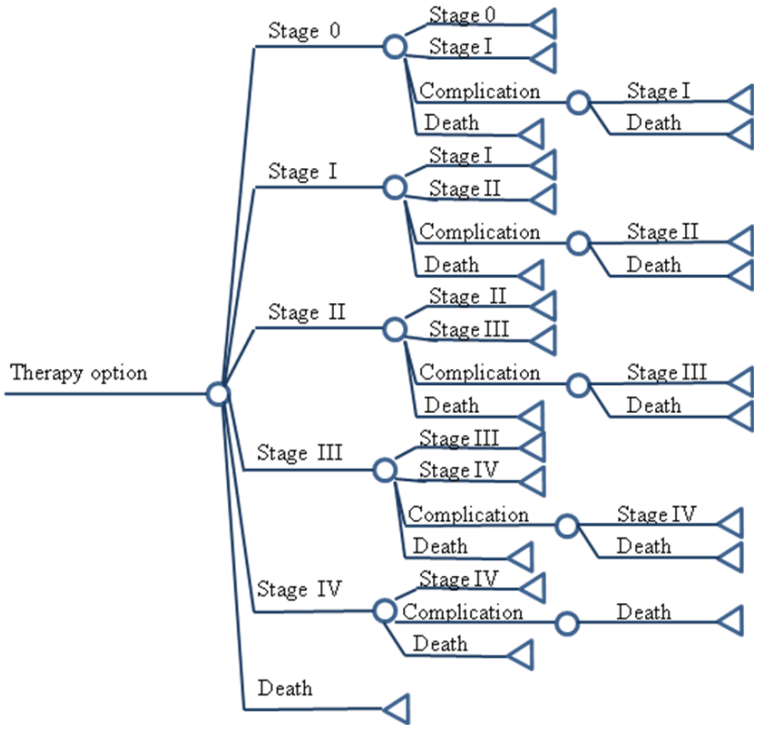

Figure 8: Decision tree scheme for one antineoplasic systemic therapy option.

Source: Own Construct.

Each branch of the Markov node is attached to a subtree that models the possible events for each Markov stage. All therapy related **complications (namely ARF, AHF, APD, ACVD, osteoporosis, AAE, AC** and **AD)** may be either **fatal** or **non-fatal.** If **non-fatal,** the patient is considered to progress to the next stage of disease, because usually the antineoplasic therapy must be interrupted for a period of time and the disease severeness increases.

Death, which include the chance of dying from all causes, is the terminal node. For example, a strategy involving systemic antineoplasic therapy may model the events of death due to the disease, therapeutical complications, and various outcomes of the treatment itself, which are simulated. A patient who dies during one cycle will begin the next cycle in the *dead stage.* For patients who do not die, the next chance node models the chance of progressing through disease stages.

For practical reasons, the analysis must be restricted to a finite time frame, often referred to as the ***time horizon*** of the analysis, which will be mentioned next.
This means that, aside from death, the outcomes of each tree branch are represented by terminal nodes that may not be final outcomes, but may simply represent convenient stopping points for the scope of the analysis. Thus, every tree contains terminal nodes that represent "subsequent prognosis" for a particular combination of patient characteristics and events.

In the CHEUAL model, we will choose between the most cost-effective systemic therapy option for BC treatment. To be complete, the decision tree must be represented as follows:

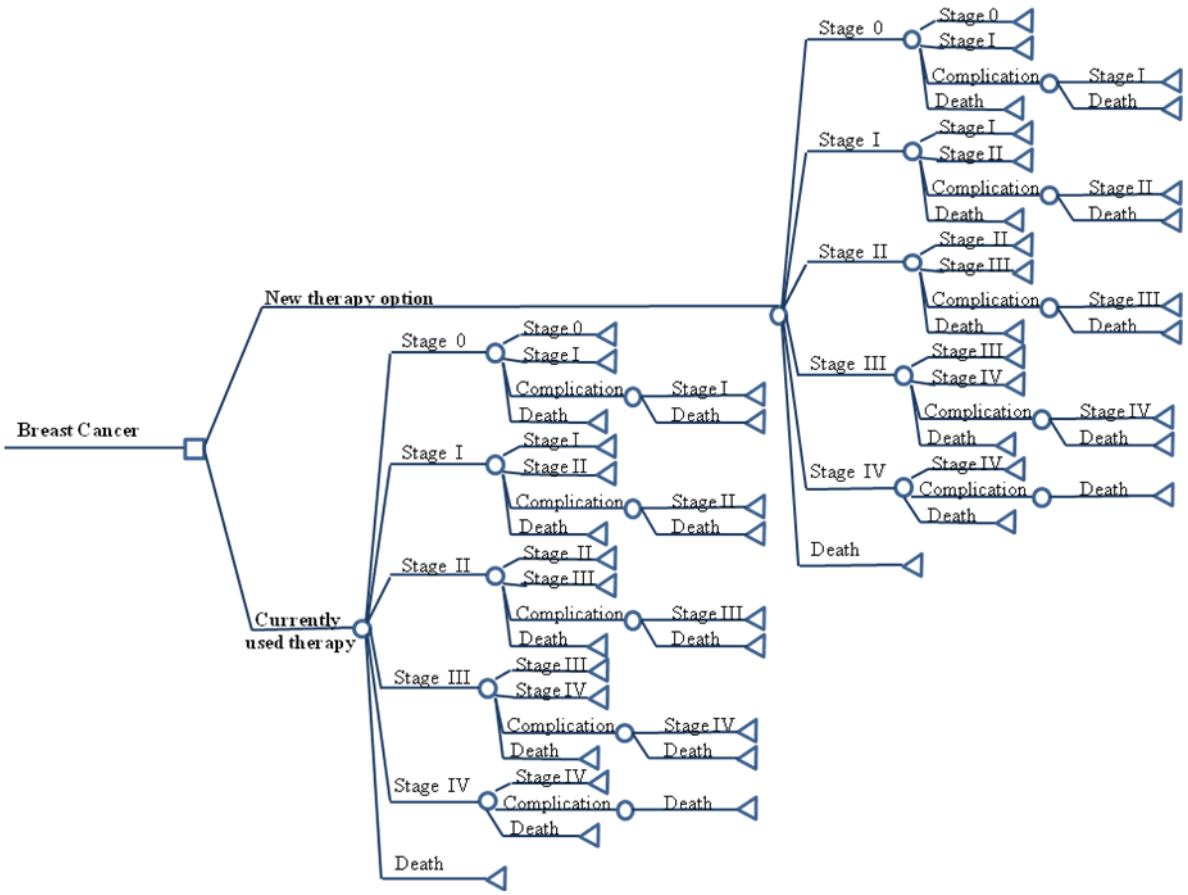

Figure 9: Complete decision tree scheme for alternative antineoplasic systemic BC treatment options.
Source: Own construct.

There are various ways in which a decision analyst can assign values to the terminal nodes of the decision tree. In some cases the outcome measure is a crude life expectancy; in others, as in this particular study, they are QALYs and costs, that are subject of determination for each branch.

2.3.2.2.5.3.2. TIME HORIZON OF THE STUDY & CYCLE LENGTH

The **time horizon of the study** should be considered (Dedes *et al.*, 2009; Liberato, Marchetti & Barrosi, 2007) and is a variable of utmost importance. As described, the comparison of the therapeutic alternatives must be based on all its costs and consequences, regardless of when they occur. Hence, the horizon of the study should match the time period in which there are costs and consequences attributable to

treatment. However, there are situations where this implies unreasonably lengthen the period of reference without resulting in significant benefit to the accuracy of the study. Rather, consideration of a long time horizon may be a factor of less accurate results because the randomness of the estimates increases with the extension of the term of reference. Thus, it is assumed that in these cases, the time horizon of the study is limited by the use of models, with inclusion of the methodology and all the assumptions on which had been relied for its construction (Silva *et al*., 1998).

Considering the reasons presented, we think that the time horizon most suitable to this study is of 120 month (ten years), regarding that the *per os* therapy should have a minimum duration of five years, usually after six month of chemotherapy drugs cycles; and that paclitaxel is administrated for only four month, although patients must be followed by six years after the ending of the cycle (INFARMED, 2010) due to long-term probable complications. The time left from both situations is thought considered to be sufficient to adverse effects/ disease complications due to therapy manifest themselves. On the other hand, it is well known that after 10 years of stable stage disease after surgery or recurrence, patients are considered to be "cured" (Karnon *et al*., 2006)

Before probabilities can be assigned, the analyst must decide on the cycle length. The **length of the cycle of the model** is chosen to represent a clinically meaningful time interval. If the time frame is shorter than the lifetime of the patient or if model events may occur very frequently, the cycle length of time must be shorter. The cycle must also be shorter if a rate changes rapidly over time length. An example is the risk of myocardial infarction (MI) following a chemotherapy cycle, which lasts six months, especially if the patient has a previous history of cardiovascular disease. The rapidity of this change in risk dictates a monthly cycle time length. Other relevant consideration is that the cohort simulation is an approximation and will more closely approximate the "exact" solution when the cycle length is short, reinforcing the presented idea.

In practice, often the choice of a cycle time length will be determined by the available probability data. For example, if only yearly probabilities are available, there is little advantage of using a monthly cycle length (Sonnenberg & Beck, 1993).

For this reason and since we are considering current chemotherapy cycles of six month, time needed to a complete FEC and TAC treatments, we will also chose to consider the

model cycle length of six month. Note that immunomodulators therapy cycle lasts for a year and that tamoxifen and letrozole must be administrated at least during 5 years. We must also note that although paclitaxel therapy cycle is of only four month, all of the therapy considered has high incidence of adverse effects. We think that the most adequate solution was to account for a three month cycle length, to better evaluate how patient's health stage is at each time. However, we chose not to do it because we only have studies of complication annual statistics for BC treatment. On the other hand, a year cycle length is regard to be too much because of the aggressiveness of treatment, which as the ability to alter the health of the patient in a short period of time. Patients who are not withdrawn from therapy because of severe cumulative toxicities remained in the stable disease stages for the median duration of response and then, may develop progressive disease (Brown, Lipscomb & Snyder, 2001).

Considering all of these variables, **a cycle length of six month during a time horizon of 120 month, means that our model will have 20 cycles per therapy option**.

Despite the relatively simple decision tree previously presented in Figure n.8 and carrying out the recursion for only one time period, the tree is "bushy," with 24 terminal branches for each cycle of only one therapy option.
If each therapeutic option that is being compared has a *twenty* cycle model, and keeping in mind that we will compare *two* therapeutical options from *three* different perspectives, of *two* age intervals and *two* tumor types, the resultant tree would have thousands of terminal branches, namely 11.520 branches (2x20x24x3x2x2) . Thus, a recursive model is tractable for only a very short time horizon, which is not the case, being therefore inappropriate to this study. Trying to fulfill this gap, we decided to use a Markov Model.

2.3.2.2.5.3.3. MARKOV MODEL

This work explores the method of a **Markov Model for estimating consequences and costs**. Markov models were first developed by Andrei Markov (1856-1922) and are partially cyclic direct graphs (Stahl, 2008).

In 1983, Beck and Pauker described the use of Markov models for determining prognosis in medical applications.

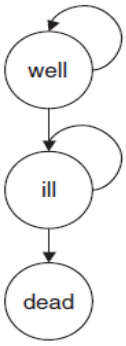

Figure n. 10: Markov Model Example.
Source: Stahl (2008).

Since that introduction, Markov models have been applied with increasing frequency in published decision analyses. Even a microcomputer software has been developed to allow constructing and evaluating Markov models more easily (Sonnenberg & Beck, 1993). For these reasons, a revisit of the Markov model is timely.

Markov models are particularly useful when a decision problem involves a risk that is ongoing over time, for example, for developing disease complications or therapy adverse effects.

There are two important consequences of events that have ongoing risk:

First, the times at which the events will occur are uncertain. This has important implications because the utility of an outcome often depends on when it occurs. For example, a metastasis dissemination that occurs immediately may have a different impact on the patient than one that occurs five years later. For economic analyses, both costs and utilities are discounted such that later events have less impact than earlier ones, as we shall see ahead.

The second consequence is that a given event may occur more than once and events that are repetitive or that occur with uncertain timing are difficult to track using a simple Markov model.

Markov processes are categorized according to whether the stage-transition probabilities are constant over time or not.

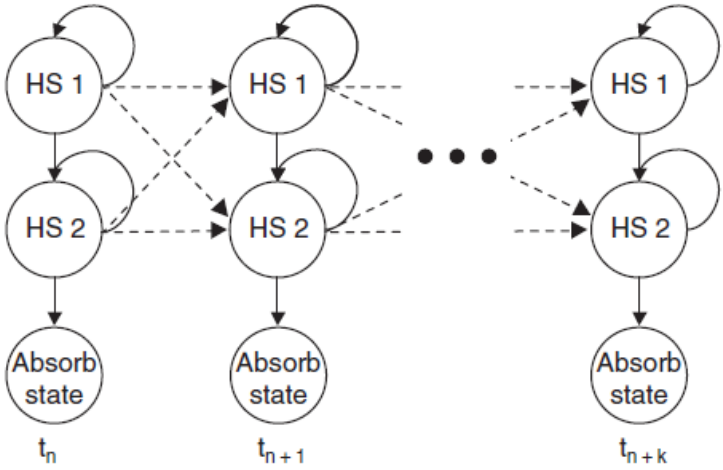

Figure n.11: Markov decision process.

Source: Stahl (2008).

Most Markov models used in healthcare are **semi-Markov stage transition models**, which are a general type of **Markov decision process**, were the transition probabilities are allowed to vary or to be time-variant and usually need to be solved numerically via simulation (Stahl, 2008).

For example, the transition probability for the transition from *well to dead* consists of two components:

- The first component is the probability of dying from unrelated causes. In general, this probability changes over time because, as the patient gets older, the probability of dying from unrelated causes will increase continuously;
- The second component is the probability of suffering a fatal complication during the cycle. This may or may not be constant over time.

A special type of Markov process, in which the transition probabilities are constant over time and can be solved analytically, is called a **Markov chain**. The structure of a Markov Chain is similar to Markov´s decision processes (that describe and analyze sequential decisions under conditions of uncertainty), except that the transition matrix doesn´t depend on the actions or policy of the decision maker at each time increment. Unlike the Markov Decision Process, in the Markov chain, the decision rule policy is stationary, meaning that the decision rules remain constant for all time (Stahl, 2008).

The model chosen to our study is a **Semi-Markov Stages Transition Model**, although we had considered two age intervals, trying to overcome the gap due to age related life expectancy and disease complication history differences, as previously described.
After a course of the specified treatment, the model determines the progression through health stages over time based on transition probabilities equations constructed based on published data, or as fixed incremental adjustments every semester (in the absence of any relevant published data), as previously done by Palmer *et al.* (2004[a]). At the time of cycle transition, patients could die directly, became stable or progress to a different disease stage until palliation stage and death, like presented in the next figure.

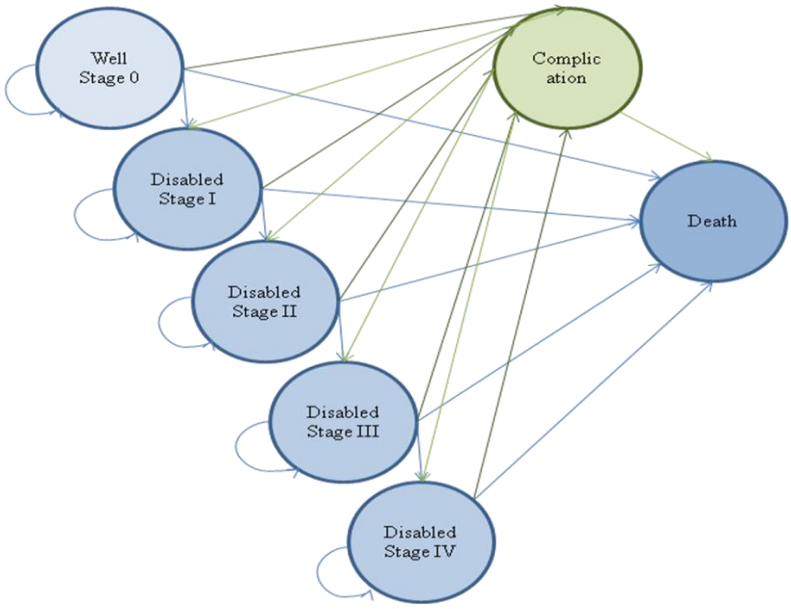

Figure 12: Stage-Transition Diagram representing the Markov Process of the CHEUAL BC Model.
Source: Own construct.

Regarding the decision tree previously presented, a **Markov model** provides a far more convenient way of modeling prognosis for clinical problems with ongoing risk. The model assumes that the patient is always in one of a finite number of six stages of health referred to as **Markov stages** (in blue). All events of interest are modeled as transitions from one stage to another. Each stage is assigned an utility and cost, and the contribution of this variables to the overall prognosis depends on the length of time spent in it.

As presented before, the time horizon of the analysis is divided into equal increments of time, referred to as ***Markov cycles***. During each cycle, the patient may make a transition from one stage to another. Figure n. 12 shows a commonly used representation of Markov processes, called a **stage-transition diagram,** in which each stage is represented by a circle.

Note that complications are a *temporary stage*, assumed to make part of the stage transition diagram. However, this wasn´t considered a *health stage* because we assumed that people only stay in that stage for a short time period, not completing a six month cycle length. Furthermore, this transition stage has great impact on health stage evolution progression, since has a related specific mortality rate (most of the time) and because imposes the stop of chemotherapy treatment, reason why each time patients develop complications are assumed to progress to the next BC disease stage.

Arrows connecting two different stages indicate allowed transitions. Arrows leading from a stage to itself indicate that the patient may remain in that stage in consecutive cycles. Only certain transitions are allowed. For example, transition from *disabled to well***,** or from a more severe stage of disease to a previous one, are not allowed. A person in either the *well stage* or in any of the *disabled states* may die and thus make a transition to the *dead stage*. However, a person who is in the *dead stage*, obviously, cannot make a transition to any other stage during a cycle (Sonnenberg & Beck, 1993).

Markov process decision models had also been presented in the studies of Dedes *et al*. (2009); Karnon *et al.* (2006); Welsing, Severens, Hartman, Gestel, Riel, & Laan (2006); Mansel, Locker, Fallowfield, Benedict & Jones (2007); Quagari, Karnon, Delea, Talbot & Brandman (2007); Lundkvist, Wilking, Holmberg, & Jonsson (2007); Shiroiwa, Fukuda, Shimozuma, Ohashi, & Tsutani (2008); Garrison, Lubeck, Lalla, Paton, Dueck, & Perez (2007); Lidgren, Jonsson, Rehnberg, Wilking & Bergh (2008); and Thompson, Taylor, Montoya, Winer, Jones & Weinstein (2007).

For example, Dedes *et al*. (2009) considers the existence of three mutually exclusive health stages: stable/ responsive disease, disease progression and death. Like in the study of Karnon *et al.* (2006), *stable disease* patients were assumed to be at risk of progression (to a LRR of primary disease or a new primary tumor in the contralateral breast) or to remain in the stable stage for 10 years after the initial diagnosis,

contralateral tumor or LRR, period after which women are assumed to be disease free. *Progression* patients were assumed to be at risk of distant metastasis recurrence (bone, visceral (lung, liver or pleural effusion) and soft tissue (all other sites)) and/or dying from the disease. All patients were assumed to be at risk of death from non-breast cancer related causes.

At model entry, all the patients were in the stable/responsive disease stage and at the end of each cycle, they could remain stable, develop disease progression, or die.
For a disease in which length of survival is not significantly increased with treatment, like metastatic BC, it is reasonable to assume that patients who respond to treatment incur a lower cost than patients who experience disease progression, since disease progression often involves additional therapy to alleviate symptoms and disease control. Similarly, **patients who respond to therapy** are assumed to have a better quality of life than patients who progress, since patients who respond spend longer in better states of health. **Patients who experience adverse effects from therapy** are assumed to have a reduced quality of life at that time and to incur additional costs related to clinical management of the adverse effect (Brown, Lipscomb & Snyder, 2001), especially if previous related disease history.

Note that there are **several shortcomings within this model**. First, the model does not specify when events occur. Second, the structure implies that complication may occur only once per-cycle per disease stage, when, in fact, they may occur more than once.
The first problem, specifying when events occur, may be addressed by making the assumption that complication occurs at the average time consistent with the known rate of each complication. For example, if the rate of an ACVE is a constant 0,05 per person per year, then the average time before the occurrence of an ischemic episode is 1/0,05 or 20 years. Thus, the event of having a fatal ACVE will be associated with a utility of 20 years of normal-quality survival (Sonnenberg & Beck, 1993). However, the patients normal life expectancy may be less than 20 years, which is a limitation of this model that has a time horizon inferior to this period.
Both the timing of events and respective representation may occur more than once. Each repetition of the structure represents a convenient length of time and any event may be considered repeatedly.

The availability of specialized software to evaluate Markov processes have resulted in greater reliance on Markov processes, with time-variant probabilities. However, we chose to develop manually the correspondent Markov matrix at this time, considering all the variables inserted alongside.

2.3.2.2.5.3.3. 1. MARKOV BC TRANSITION PROBABILITY: ASSIGNMENT OF PROBABILITIES

The net probability of making a transition from one stage to another during a single cycle is called **transition probability.** The Markov process is completely defined by the probability distribution among the starting stages and the probabilities for the individual allowed transitions. For a Markov model of *n* stages, there will be at least n^2 transition probabilities (Stahl, 2008).
We considered that probabilities varied in respect to time and to "temporary stages", that are related to disease/therapy complications. Probabilities representing disallowed transitions will, of course, be zero. The matrix solution of Markov processes were described in detail by Beck and Pauker (1983).

The model illustrated in figure 12 is compatible with a number of different models collectively referred to as *finite stochastic processes.*
In order for a Markov process to terminate, it must have at least one stage that the patient cannot leave. Such stages are called *absorbing stages* because, after a sufficient number of cycles have passed in a closed matrix, the entire cohort will have been absorbed by those stages. In medical examples, the absorbing states must represent death, because it is the only stage a patient cannot leave. There is usually no need for more than one dead stage, because the incremental utility for the dead stage is zero. However, if one wishes to keep track of the causes of death, then more than one dead stage may be used, which is not the case in this study.
Temporary stages are required whenever there is an event that has only short-term effects. Such stages are defined as having transitions only to other stages and not to themselves. This guarantees that the patient can spend, at most, one cycle in that stage.

Like illustrated in figure 12 (and previously described), the temporary stage added, was labeled *complications stage*. An arrow leads to *complications* from the *well* and from all the *disabled stages*, and there is no arrow from the c*omplication* back to itself. This ensures that a patient may spend no more than a single cycle in the *complication stage*.
Temporary stages have two uses. The first use is to apply a utility or cost adjustment specific to the temporary stage for a single cycle. The second use is to assign temporarily different transition probabilities. For example, the probability of *death* may be higher in the *complication stage* than in either the *well stage* or any of the *disabled stages*.

If models represent a Markov process, one additional restriction applies. This restriction, sometimes referred to as the ***Markovian assumption*** or the ***Markov property,*** specifies that the behavior of the process subsequent to any cycle depends only on its description in that cycle. That is, the process has no memory for earlier cycles (Beck and Pauker, 1983). Thus, in our example, if someone is in the *disabled stage IV* after cycle *n*, we know that the probability of the patient to end up in the *dead stage* is after cycle *n* + **1.** It does not matter how much time the person spent in the *well stage* before becoming *disabled stage I*, nor how much time it took to achieve *disabled stage IV*. Put in another way, all patients in the *disabled stage IV* have the same prognosis regardless of their previous histories.
For this reason, a separate stage must be created for each subset of the cohort, with distinct utility or prognosis and cost, as we have done with the "*complications stage*", which represents all the complications previously described.

However, an acute complication event can lead directly to *death*, although people might also die from other different causes, as in a car accident, for example.
This means that the Markovian assumption is not followed strictly in medical problems. However, the assumption is necessary in order to model prognosis with a finite number of stages (Stahl, 2008).

Trying to summarize every variable we need to considered in a Markov matrix, we developed the **BC transition stages probability CHEUAL model**, from three different study perspectives, represented by the following tables (22, 23 and 24, respectively).

The first task was to assign probabilities to different Markov stages, regarding: BC incidence of each stage, age groups, tumor type, previous history of disease related to probable therapy complication events (of none, one or two diseases) and complication incidence at each BC stage. As we intended to built an opened matrix, in each cycle (with exception of the first), BC and complication prevalence, as well as mortality rate non-related to BC, were contemplated.
Recall that these probabilities represent the probabilities of starting in the individual stages.

24-64 years Female Gender HER+/ER-
No previous History of Complications

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00025	0,00025	0,00025	0,00026	0,00026	0,00027	0,00027	0,00027	0,00028	0,00028	0,00029	0,00029	0,00029	0,00030	0,00030	0,00031	0,00031	0,00031	0,00032	0,00032	0,00264	0,00568
I	0,05363	0,05541	0,05381	0,05569	0,05890	0,06116	0,06289	0,06463	0,06637	0,06811	0,06985	0,07159	0,07333	0,07507	0,07681	0,07855	0,08029	0,08203	0,08377	0,08551	0,60059	1,37737
II	0,13432	0,13776	0,13216	0,13711	0,14583	0,15190	0,15616	0,16048	0,16480	0,16912	0,17344	0,17776	0,18208	0,18640	0,19071	0,19503	0,19935	0,20367	0,20799	0,21231	1,48962	3,41836
III	0,03961	0,04109	0,05186	0,05132	0,04926	0,04952	0,05108	0,05248	0,05390	0,05532	0,05673	0,05815	0,05956	0,06098	0,06240	0,06381	0,06523	0,06665	0,06806	0,06948	0,49542	1,12647
IV	0,01820	0,01925	0,02308	0,02472	0,02290	0,02258	0,02322	0,02387	0,02451	0,02516	0,02580	0,02645	0,02709	0,02774	0,02838	0,02902	0,02967	0,03031	0,03096	0,03160	0,22749	0,51452
Death	1,28899	1,33179	1,38351	1,42665	1,46550	1,50651	1,54941	1,59230	1,63520	1,67810	1,72100	1,76390	1,80680	1,84969	1,89259	1,93549	1,97839	2,02129	2,06419	2,10708	14,85795	33,99838

Table n. 22.1: BC Stage Probability Matrix: Current Therapy - **Oncologist Perspective** (Summary). Source: Own production.

24-64 years Female Gender HER-/ER+
No previous History of Complications

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00025	0,00025	0,00025	0,00026	0,00026	0,00027	0,00027	0,00027	0,00028	0,00028	0,00029	0,00029	0,00029	0,00030	0,00030	0,00031	0,00031	0,00031	0,00032	0,00032	0,00264	0,00568
I	0,05363	0,05541	0,05506	0,05686	0,05857	0,06028	0,06200	0,06371	0,06543	0,06714	0,12248	0,06851	0,07340	0,07507	0,07681	0,07855	0,08029	0,08203	0,08377	0,08551	0,59808	1,42449
II	0,13432	0,13776	0,13629	0,15421	0,14418	0,14937	0,15355	0,15780	0,16205	0,16629	0,17054	0,17684	0,18204	0,18640	0,19071	0,19503	0,19935	0,20367	0,20799	0,21231	1,49583	3,42074
III	0,03961	0,04109	0,04896	0,04973	0,05218	0,05269	0,05432	0,05582	0,05733	0,05883	0,06034	0,06185	0,05932	0,06099	0,06240	0,06381	0,06523	0,06665	0,06806	0,06948	0,51054	1,14867
IV	0,01820	0,01925	0,02059	0,02156	0,02215	0,02286	0,02345	0,02411	0,02476	0,02541	0,02607	0,02672	0,02728	0,02771	0,02838	0,02902	0,02967	0,03031	0,03096	0,03160	0,22237	0,51009
Death	1,28899	1,33179	1,37886	1,42181	1,46474	1,50767	1,55061	1,59354	1,22864	1,67809	1,72233	1,76527	1,80658	1,84947	1,89236	1,93525	1,97815	2,02104	2,06393	2,10682	14,44474	33,58594

Table n. 22.2: BC Stage Probability Matrix: Current Therapy - **Oncologist Perspective** (Summary). Source: Own production.

≥ 65 years Female Gender HER+/ER-
No previous History of Complications

	Cycles																				Acumul Total 5years	Acumul Total 10years
BC Stages	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20		
0	0,00025	0,00025	0,00025	0,00026	0,00026	0,00027	0,00027	0,00027	0,00028	0,00028	0,00029	0,00029	0,00029	0,00030	0,00030	0,00031	0,00031	0,00031	0,00032	0,00032	0,00264	0,00568
I	0,05363	0,05541	0,05381	0,05569	0,05890	0,06057	0,06290	0,06463	0,06637	0,06811	0,06985	0,07159	0,07333	0,07507	0,07681	0,07855	0,08029	0,08203	0,31523	0,08012	0,60002	1,60287
II	0,13432	0,13776	0,13216	0,13711	0,14583	0,14988	0,15623	0,16048	0,16480	0,16912	0,17344	0,17776	0,18208	0,18640	0,19071	0,19503	0,19935	0,19030	0,20855	0,21767	1,48767	3,40895
III	0,03961	0,04109	0,05186	0,05132	0,04926	0,04632	0,05117	0,05248	0,05390	0,05532	0,05673	0,05815	0,05956	0,06098	0,06240	0,06381	0,06523	0,06665	0,06750	0,06953	0,49231	1,12286
IV	0,01820	0,01925	0,02308	0,02472	0,02290	0,02346	0,02299	0,02389	0,02451	0,02516	0,02580	0,02645	0,02709	0,02774	0,02838	0,02902	0,02967	0,03031	0,03096	0,03157	0,22816	0,51515
Death	8,79701	9,08907	9,44205	9,73648	10,00161	10,29466	10,57430	10,86704	11,15981	11,45258	11,74535	12,03812	12,33089	12,62366	12,91643	13,20920	13,50197	13,79474	14,08751	14,38028	101,41462	232,04276

Table n. 22.3: BC Stage Probability Matrix: Current Therapy - **Oncologist Perspective** (Summary). Source: Own production.

≥ 65 years Female Gender HER-/ER+
No previous History of Complications

	Cycles																				Acumul Total 5years	Acumul Total 10years
BC Stages	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20		
0	0,00025	0,00025	0,00025	0,00026	0,00026	0,00027	0,00027	0,00027	0,00028	0,00028	0,00029	0,00029	0,00029	0,00030	0,00030	0,00031	0,00031	0,00031	0,00032	0,00032	0,00264	0,00568
I	0,05363	0,05541	0,05506	0,05686	0,05857	0,06028	0,06200	0,06371	0,06543	0,06714	0,12248	0,06851	0,07340	0,07507	0,07681	0,07855	0,08029	0,08203	0,08377	0,05168	0,59808	1,39066
II	0,13432	0,13776	0,13629	0,14084	0,14507	0,14931	0,15356	0,15780	0,16205	0,16629	0,17054	0,17684	0,18204	0,18640	0,19071	0,19503	0,19935	0,20367	0,20799	0,21231	1,48328	3,40819
III	0,03961	0,04109	0,04896	0,04973	0,05130	0,05280	0,05431	0,05582	0,05733	0,05883	0,06034	0,06185	0,05932	0,06099	0,06240	0,06381	0,06523	0,06665	0,06806	0,06948	0,50976	1,14789
IV	0,01820	0,01925	0,02059	0,02156	0,02215	0,02281	0,02346	0,02411	0,02476	0,02541	0,02607	0,02672	0,02728	0,02771	0,02838	0,02902	0,02967	0,03031	0,03096	0,03160	0,22233	0,51005
Death	8,79701	9,08907	9,41037	9,70346	9,99646	10,28947	10,58247	10,87547	11,16848	11,46148	11,75448	12,04748	12,33091	12,62366	12,91643	13,20757	13,50030	13,79303	14,08577	14,37850	101,37373	232,01187

Table n. 22.4: BC Stage Probability Matrix: Current Therapy - **Oncologist Perspective** (Summary). Source: Own production.

24-64 years Female Gender HER+/ER-
Previous History of One Complication

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00014	0,00014	0,00014	0,00014	0,00014	0,00014	0,00015	0,00015	0,00015	0,00015	0,00015	0,00015	0,00015	0,00016	0,00016	0,00016	0,00016	0,00016	0,00016	0,00016	0,00144	0,00301
I	0,03019	0,02886	0,02991	0,03083	0,03284	0,03376	0,03518	0,03614	0,03711	0,03808	0,03906	0,04003	0,04100	0,04198	0,04295	0,04392	0,04489	0,04587	0,04684	0,04781	0,33290	0,76725
II	0,07562	0,07132	0,07404	0,07629	0,08158	0,08380	0,08756	0,08993	0,09235	0,09477	0,09719	0,09961	0,10203	0,10445	0,10687	0,10929	0,11171	0,11413	0,11655	0,11897	0,82725	1,90804
III	0,02230	0,02917	0,02869	0,02983	0,02812	0,02939	0,02901	0,02996	0,03076	0,03157	0,03237	0,03318	0,03399	0,03480	0,03561	0,03642	0,03723	0,03803	0,03884	0,03965	0,28879	0,64892
IV	0,01025	0,01271	0,01398	0,01416	0,01246	0,01347	0,01318	0,01352	0,01390	0,01426	0,01463	0,01499	0,01536	0,01572	0,01609	0,01645	0,01682	0,01718	0,01755	0,01791	0,13190	0,29461
Death	0,72571	0,75959	0,78474	0,80919	0,82866	0,85291	0,87502	0,89924	0,92347	0,94770	0,97193	0,99616	1,02038	1,04461	1,06884	1,09307	1,11730	1,14153	1,16576	1,18998	8,40623	19,21579

Table n. 22.5: BC Stage Probability Matrix: Current Therapy - **Oncologist Perspective** (Summary). Source: Own production.

24-64 years Female Gender HER-/ER+
Previous History of One Complication

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00014	0,00014	0,00014	0,00014	0,00014	0,00014	0,00015	0,00015	0,00015	0,00015	0,00015	0,00015	0,00015	0,00016	0,00016	0,00016	0,00016	0,00016	0,00016	0,00016	0,00144	0,00301
I	0,03019	0,02886	0,03078	0,03168	0,03264	0,03360	0,03455	0,03551	0,03646	0,03742	0,06857	0,03784	0,04107	0,04197	0,04295	0,04392	0,04489	0,04587	0,04684	0,04781	0,33169	0,79343
II	0,07562	0,07132	0,07653	0,08626	0,08053	0,08353	0,08586	0,08823	0,09061	0,09298	0,09535	0,09922	0,10198	0,10445	0,10687	0,10929	0,11171	0,11413	0,11655	0,11897	0,83146	1,90999
III	0,02230	0,02917	0,02734	0,02861	0,03002	0,03022	0,03118	0,03204	0,03290	0,03377	0,03463	0,03550	0,03382	0,03481	0,03561	0,03642	0,03723	0,03803	0,03884	0,03965	0,29754	0,66209
IV	0,01025	0,01271	0,01197	0,01224	0,01265	0,01305	0,01338	0,01376	0,01413	0,01450	0,01487	0,01524	0,01549	0,01570	0,01609	0,01645	0,01682	0,01718	0,01755	0,01791	0,12863	0,29194
Death	0,72571	0,75959	0,77976	0,80401	0,82829	0,85257	0,87686	0,90114	0,92542	0,94970	0,97398	0,99826	1,02040	1,04461	1,06884	1,09292	1,11715	1,14137	1,16560	1,18982	8,40306	19,21602

Table n. 22.6: BC Stage Probability Matrix: Current Therapy - **Oncologist Perspective** (Summary). Source: Own production.

≥ 65 years Female Gender HER+/ER-
Previous History of One Complication

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00014	0,00014	0,00014	0,00014	0,00014	0,00014	0,00015	0,00015	0,00015	0,00015	0,00015	0,00015	0,00015	0,00016	0,00016	0,00016	0,00016	0,00016	0,00016	0,00016	0,00144	0,00301
I	0,03019	0,02886	0,02991	0,03083	0,03284	0,03376	0,03518	0,03614	0,03711	0,03808	0,03906	0,04003	0,04100	0,04198	0,04295	0,04392	0,04489	0,04587	0,17715	0,04384	0,33290	0,89359
II	0,07562	0,07132	0,07404	0,07629	0,08158	0,08380	0,08756	0,08993	0,09235	0,09477	0,09719	0,09961	0,10203	0,10445	0,10687	0,10929	0,11171	0,10660	0,11692	0,12293	0,82725	1,90484
III	0,02230	0,02917	0,02869	0,02983	0,02812	0,02939	0,02901	0,02996	0,03076	0,03157	0,03237	0,03318	0,03399	0,03480	0,03561	0,03642	0,03723	0,03803	0,03847	0,03969	0,28879	0,64859
IV	0,01025	0,01271	0,01398	0,01416	0,01246	0,01347	0,01318	0,01352	0,01390	0,01426	0,01463	0,01499	0,01536	0,01572	0,01609	0,01645	0,01682	0,01718	0,01755	0,01789	0,13190	0,29459
Death	4,95279	5,18399	5,35561	5,52249	5,65536	5,82087	5,97181	6,13708	6,30243	6,46779	6,63314	6,79849	6,96385	7,12920	7,29455	7,45991	7,62526	7,79061	7,95597	8,12132	57,37020	131,142 50

Table n. 22.7: BC Stage Probability Matrix: Current Therapy - **Oncologist Perspective** (Summary). Source: Own production.

≥ 65 years Female Gender HER-/ER+
Previous History of One Complication

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00014	0,00014	0,00014	0,00014	0,00014	0,00014	0,00015	0,00015	0,00015	0,00015	0,00015	0,00015	0,00015	0,00016	0,00016	0,00016	0,00016	0,00016	0,00016	0,00016	0,00144	0,00301
I	0,03019	0,02886	0,03078	0,03168	0,03264	0,03360	0,03455	0,03551	0,03646	0,03742	0,06857	0,03784	0,04107	0,04197	0,04295	0,04392	0,04489	0,04587	0,04684	0,04781	0,33169	0,79343
II	0,07562	0,07132	0,07653	0,07873	0,08111	0,08349	0,08586	0,08823	0,09061	0,09298	0,09535	0,09922	0,10198	0,10445	0,10687	0,10929	0,11171	0,11413	0,11655	0,11897	0,82447	1,90300
III	0,02230	0,02917	0,02734	0,02861	0,02944	0,03030	0,03117	0,03204	0,03290	0,03377	0,03463	0,03550	0,03382	0,03481	0,03561	0,03642	0,03723	0,03803	0,03884	0,03965	0,29704	0,66158
IV	0,01025	0,01271	0,01197	0,01224	0,01265	0,01301	0,01338	0,01376	0,01413	0,01450	0,01487	0,01524	0,01549	0,01570	0,01609	0,01645	0,01682	0,01718	0,01755	0,01791	0,12860	0,29191
Death	4,95279	5,18399	5,32167	5,48717	5,65288	5,81859	5,98430	6,15001	6,31572	6,48144	6,64715	6,81286	6,96393	7,12920	7,29455	7,45890	7,62423	7,78956	7,95489	8,12022	57,34855	131,144 05

Table n. 22.8: BC Stage Probability Matrix: Current Therapy - **Oncologist Perspective** (Summary). Source: Own production.

24-64 years Female Gender HER+/ER-
Previous History of Two Complications

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00119	0,00248
I	0,02518	0,01236	0,02000	0,01659	0,02340	0,02213	0,02474	0,02493	0,02572	0,02636	0,02704	0,02771	0,02838	0,02905	0,02972	0,03039	0,03106	0,03173	0,03241	0,03308	0,22143	0,52201
II	0,06306	0,02828	0,05072	0,03848	0,05908	0,05392	0,06174	0,06167	0,06384	0,06535	0,06706	0,06870	0,07037	0,07203	0,07370	0,07536	0,07702	0,07868	0,08035	0,08201	0,54614	1,29141
III	0,01860	0,05452	0,00000	0,06508	0,00748	0,04496	0,02465	0,03575	0,03215	0,03491	0,03502	0,03621	0,03697	0,03790	0,03876	0,03965	0,04053	0,04141	0,04229	0,04317	0,31809	0,71000
IV	0,00855	0,01998	0,04785	0,00000	0,04455	0,00000	0,02856	0,00898	0,02091	0,01529	0,01876	0,01776	0,01887	0,01902	0,01960	0,01999	0,02046	0,02090	0,02135	0,02179	0,19467	0,39319
Death	0,60520	0,63345	0,65442	0,67481	0,69105	0,71127	0,72971	0,74991	0,77011	0,79032	0,81052	0,83073	0,85093	0,87114	0,89134	0,91155	0,93175	0,95196	0,97217	0,99237	7,01025	16,02472

Table n. 22.9: BC Stage Probability Matrix: Current Therapy - **Oncologist Perspective** (Summary). Source: Own production.

24-64 years Female Gender HER-/ER+
Previous History of Two Complications

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00119	0,00248
I	0,02518	0,01236	0,02260	0,01990	0,02167	0,02189	0,02265	0,02322	0,02386	0,02448	0,05028	0,01702	0,03102	0,02840	0,02988	0,03035	0,03107	0,03173	0,03241	0,03308	0,21781	0,53306
II	0,06306	0,02828	0,05744	0,04854	0,05413	0,05405	0,05626	0,05752	0,05919	0,06067	0,06224	0,07246	0,06639	0,07411	0,07279	0,07572	0,07688	0,07874	0,08033	0,08201	0,53914	1,28080
III	0,01860	0,05452	0,01511	0,04384	0,03012	0,03826	0,03603	0,03851	0,03890	0,04021	0,04112	0,04220	0,03605	0,03681	0,03992	0,03889	0,04095	0,04120	0,04239	0,04313	0,35409	0,75674
IV	0,00855	0,01998	0,02031	0,00687	0,02219	0,01190	0,01891	0,01576	0,01810	0,01762	0,01854	0,01879	0,02075	0,01796	0,01960	0,02043	0,02001	0,02123	0,02114	0,02191	0,16020	0,36056
Death	0,60520	0,63345	0,65392	0,67429	0,69466	0,71102	0,73124	0,75149	0,77174	0,79199	0,81224	0,83248	0,85094	0,87114	0,89134	0,91143	0,93163	0,95183	0,97203	0,99224	7,01899	16,03630

Table n. 22.10: BC Stage Probability Matrix: Current Therapy - **Oncologist Perspective** (Summary). Source: Own production.

≥ 65 years Female Gender HER+/ER-
Previous History of Two Complications

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00119	0,00248
I	0,02518	0,01236	0,02000	0,01659	0,02340	0,02213	0,02474	0,02493	0,02572	0,02636	0,02704	0,02771	0,02838	0,02905	0,02972	0,03039	0,03106	0,03173	0,03241	0,03308	0,22143	0,52201
II	0,06306	0,02828	0,05072	0,03848	0,05908	0,05392	0,06174	0,06167	0,06384	0,06535	0,06706	0,06870	0,07037	0,07203	0,07370	0,07536	0,07702	0,07868	0,08035	0,08201	0,54614	1,29141
III	0,01860	0,05452	0,00000	0,06508	0,00748	0,04496	0,02465	0,03575	0,03215	0,03491	0,03502	0,03621	0,03697	0,03790	0,03876	0,03965	0,04053	0,04141	0,04229	0,04317	0,31809	0,71000
IV	0,00855	0,01998	0,04785	0,00000	0,04513	0,00000	0,02864	0,00894	0,02093	0,01528	0,01876	0,01776	0,01888	0,01902	0,01960	0,01999	0,02046	0,02090	0,02135	0,02179	0,19531	0,39382
Death	4,13030	4,32311	4,46623	4,60540	4,71620	4,85423	4,98010	5,11792	5,25582	5,39371	5,53161	5,66950	5,80740	5,94529	6,08318	6,22108	6,35897	6,49687	6,63476	6,77265	47,84302	109,36432

Table n. 22.11: BC Stage Probability Matrix: Current Therapy - **Oncologist Perspective** (Summary). Source: Own production.

≥ 65 years Female Gender HER-/ER+
Previous History of Two Complications

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00119	0,00248
I	0,02518	0,01236	0,02260	0,01990	0,02167	0,02189	0,02265	0,02322	0,02386	0,02448	0,02510	0,01713	0,03099	0,02841	0,02988	0,03035	0,03107	0,03173	0,03241	0,03308	0,21781	0,50796
II	0,06306	0,02828	0,05744	0,04854	0,05413	0,05405	0,05626	0,05752	0,05919	0,06067	0,06224	0,04224	0,07726	0,07021	0,07419	0,07522	0,07706	0,07867	0,08035	0,08201	0,53914	1,25858
III	0,01860	0,05452	0,01511	0,04384	0,03012	0,03826	0,03603	0,03851	0,03890	0,04021	0,04112	0,03586	0,02761	0,04391	0,03583	0,04093	0,03999	0,04163	0,04220	0,04320	0,35409	0,74637
IV	0,00855	0,01998	0,02031	0,00687	0,02219	0,01190	0,01891	0,01576	0,01810	0,01762	0,01854	0,01587	0,01946	0,01526	0,02331	0,01747	0,02191	0,02015	0,02172	0,02162	0,16020	0,35550
Death	4,13030	4,32311	4,46284	4,60185	4,74085	4,85253	4,99052	5,12871	5,26690	5,40510	5,54329	5,68148	5,80746	5,94529	6,08318	6,22024	6,35811	6,49599	6,63386	6,77174	47,90270	109,44335

Table n. 22.12: BC Stage Probability Matrix: Current Therapy - **Oncologist Perspective** (Summary). Source: Own production.

24-64 years Female Gender HER+/ER-
No previous History of Complications

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00006	0,00006	0,00006	0,00006	0,00007	0,00007	0,00007	0,00007	0,00007	0,00007	0,00007	0,00007	0,00007	0,00007	0,00008	0,00008	0,00008	0,00008	0,00008	0,00008	0,00066	0,00142
I	0,01341	0,01385	0,01345	0,01392	0,01472	0,01529	0,01572	0,01616	0,01659	0,01703	0,01746	0,01790	0,01833	0,01877	0,01920	0,01964	0,02007	0,02051	0,02094	0,02138	0,15015	0,34434
II	0,03358	0,03444	0,03304	0,03428	0,03646	0,03797	0,03904	0,04012	0,04120	0,04228	0,04336	0,04444	0,04552	0,04660	0,04768	0,04876	0,04984	0,05092	0,05200	0,24260	0,37240	1,04411
III	0,00990	0,01027	0,01296	0,01283	0,01232	0,01238	0,01277	0,01312	0,01347	0,01383	0,01418	0,01454	0,01489	0,01525	0,01560	0,01595	0,01631	0,01666	0,01702	0,01737	0,12386	0,28162
IV	0,00455	0,00481	0,00577	0,00618	0,00572	0,00565	0,00580	0,00597	0,00613	0,00629	0,00645	0,00661	0,00677	0,00693	0,00710	0,00726	0,00742	0,00758	0,00774	0,00790	0,05687	0,12863
Death	0,32225	0,33295	0,34588	0,35666	0,36637	0,37663	0,38735	0,39808	0,40880	0,41953	0,43025	0,44097	0,45170	0,46242	0,47315	0,48387	0,49460	0,50532	0,51605	0,52677	3,71449	8,49959

Table n. 23.1: BC Stage Probability Matrix: Current Therapy - **Hospital Perspective** (Summary). Source: Own production.

24-64 years Female Gender HER-/ER+
No previous History of Complications

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00018	0,00019	0,00019	0,00019	0,00020	0,00020	0,00020	0,00021	0,00021	0,00021	0,00021	0,00022	0,00022	0,00022	0,00023	0,00023	0,00023	0,00024	0,00024	0,00024	0,00198	0,00426
I	0,04022	0,04156	0,04130	0,04264	0,04393	0,04521	0,04650	0,04778	0,04907	0,05036	0,09186	0,05138	0,05505	0,05630	0,05761	0,05891	0,06022	0,06152	0,06283	0,06413	0,44856	1,06837
II	0,10074	0,10332	0,10222	0,11566	0,10814	0,11203	0,11517	0,11835	0,12154	0,12472	0,12791	0,13263	0,13653	0,13980	0,14304	0,14628	0,14952	0,15276	0,15599	0,15923	1,12188	2,56555
III	0,02970	0,03082	0,03672	0,03730	0,03913	0,03952	0,04074	0,04186	0,04299	0,04413	0,04526	0,04639	0,04449	0,04574	0,04680	0,04786	0,04892	0,04998	0,05105	0,05211	0,38291	0,86150
IV	0,01365	0,01444	0,01544	0,01617	0,01661	0,01715	0,01759	0,01809	0,01857	0,01906	0,01955	0,02004	0,02046	0,02078	0,02129	0,02177	0,02225	0,02273	0,02322	0,02370	0,16678	0,38257
Death	0,96674	0,99884	1,03415	1,06636	1,09856	1,13076	1,16296	1,19515	1,22735	1,25955	1,29175	1,32395	1,35493	1,38710	1,41927	1,45144	1,48361	1,51578	1,54795	1,58012	11,14042	25,49632

Table n. 23.2: BC Stage Probability Matrix: Current Therapy - **Hospital Perspective** (Summary). Source: Own production.

≥ 65 years Female Gender HER+/ER-
No previous History of Complications

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00006	0,00006	0,00006	0,00006	0,00007	0,00007	0,00007	0,00007	0,00007	0,00007	0,00007	0,00007	0,00007	0,00007	0,00008	0,00008	0,00008	0,00008	0,00008	0,00008	0,00066	0,00142
I	0,01341	0,01385	0,01345	0,01392	0,01472	0,01529	0,01572	0,01616	0,01659	0,01703	0,01746	0,01790	0,01833	0,01877	0,01920	0,01964	0,02007	0,02051	0,02094	0,02138	0,15015	0,34434
II	0,03358	0,03444	0,03304	0,03428	0,03646	0,03797	0,03904	0,04012	0,04120	0,04228	0,04336	0,04444	0,04552	0,04660	0,04768	0,04876	0,04984	0,05092	0,05200	0,05308	0,37240	0,85459
III	0,00990	0,01027	0,01296	0,01283	0,01232	0,01238	0,01277	0,01312	0,01347	0,01383	0,01418	0,01454	0,01489	0,01525	0,01560	0,01595	0,01631	0,01666	0,01702	0,01737	0,12386	0,28162
IV	0,00455	0,00481	0,00577	0,00618	0,00572	0,00565	0,00580	0,00597	0,00613	0,00629	0,00645	0,00661	0,00677	0,00693	0,00710	0,00726	0,00742	0,00758	0,00774	0,00790	0,05687	0,12863
Death	2,19925	2,27227	2,36051	2,43412	2,50040	2,57038	2,64357	2,71676	2,78995	2,86315	2,93634	3,00953	3,08272	3,15591	3,22911	3,30230	3,37549	3,44868	3,52188	3,59507	25,35036	58,00740

Table n. 23.3: BC Stage Probability Matrix: Current Therapy - **Hospital Perspective** (Summary). Source: Own production.

≥ 65 years Female Gender HER-/ER+
No previous History of Complications

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00018	0,00019	0,00019	0,00019	0,00020	0,00020	0,00020	0,00021	0,00021	0,00021	0,00021	0,00022	0,00022	0,00022	0,00023	0,00023	0,00023	0,00024	0,00024	0,00024	0,00198	0,00426
I	0,04022	0,04156	0,04130	0,04264	0,04393	0,04521	0,04650	0,04778	0,04907	0,05036	0,09186	0,05138	0,05505	0,05630	0,05761	0,05891	0,06022	0,06152	0,06283	0,06413	0,44856	1,06837
II	0,10074	0,10332	0,10222	0,11566	0,10814	0,11203	0,11517	0,11835	0,12154	0,12472	0,12791	0,13263	0,13653	0,13980	0,14304	0,14628	0,14952	0,15276	0,15599	0,15923	1,12188	2,56555
III	0,02970	0,03082	0,03672	0,03730	0,03913	0,03952	0,04074	0,04186	0,04299	0,04413	0,04526	0,04639	0,04449	0,04574	0,04680	0,04786	0,04892	0,04998	0,05105	0,05211	0,38291	0,86150
IV	0,01365	0,01444	0,01544	0,01617	0,01661	0,01715	0,01759	0,01809	0,01857	0,01906	0,01955	0,02004	0,02046	0,02078	0,02129	0,02177	0,02225	0,02273	0,02322	0,02370	0,16678	0,38257
Death	6,59776	6,81680	7,05777	7,27759	7,49735	7,71710	7,93685	8,15660	8,37636	8,59611	8,81586	9,03561	9,24705	9,46658	9,68613	9,90568	10,12523	10,34478	10,56432	10,78387	76,03030	174,00540

Table n. 23.4: BC Stage Probability Matrix: Current Therapy - **Hospital Perspective** (Summary). Source: Own production.

24-64 years Female Gender HER+/ER-
Previous History of One Complication

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00003	0,00003	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00036	0,00075
I	0,00755	0,00721	0,00748	0,00771	0,00821	0,00844	0,00880	0,00903	0,00928	0,00952	0,00976	0,01001	0,01025	0,01049	0,01074	0,01098	0,01122	0,01147	0,01171	0,01195	0,08323	0,19181
II	0,01891	0,01783	0,01851	0,01907	0,02039	0,02095	0,02189	0,02248	0,02309	0,02369	0,02430	0,02490	0,02551	0,02611	0,02672	0,02669	0,02796	0,02853	0,02914	0,02974	0,20681	0,47641
III	0,00557	0,00729	0,00717	0,00746	0,00703	0,00735	0,00725	0,00749	0,00769	0,00789	0,00809	0,00830	0,00850	0,00870	0,00890	0,00910	0,00928	0,00951	0,00971	0,00991	0,07220	0,16220
IV	0,00256	0,00318	0,00350	0,00354	0,00312	0,00337	0,00330	0,00338	0,00347	0,00357	0,00366	0,00375	0,00384	0,00393	0,00402	0,00411	0,00420	0,00429	0,00439	0,00448	0,03298	0,07365
Death	0,18143	0,18990	0,19618	0,20230	0,20716	0,21323	0,21876	0,22481	0,23087	0,23692	0,24298	0,24904	0,25510	0,26115	0,26721	0,27327	0,27932	0,28538	0,29144	0,29750	2,10156	4,80395

Table n. 23.5: BC Stage Probability Matrix: Current Therapy - **Hospital Perspective** (Summary). Source: Own production.

24-64 years Female Gender HER-/ER+
Previous History of One Complication

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00010	0,00010	0,00011	0,00011	0,00011	0,00011	0,00011	0,00011	0,00011	0,00011	0,00011	0,00011	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00108	0,00226
I	0,02264	0,02164	0,02308	0,02376	0,02448	0,02520	0,02591	0,02663	0,02735	0,02806	0,05142	0,02838	0,03080	0,03148	0,03221	0,03294	0,03367	0,03440	0,03513	0,03586	0,24877	0,59507
II	0,05672	0,05349	0,05740	0,06470	0,06040	0,06265	0,06439	0,06617	0,06795	0,06973	0,07151	0,07441	0,07649	0,07834	0,08015	0,08197	0,08378	0,08560	0,08741	0,08923	0,62360	1,43249
III	0,01672	0,02188	0,02051	0,02146	0,02252	0,02266	0,02338	0,02403	0,02468	0,02533	0,02598	0,02663	0,02537	0,02611	0,02671	0,02731	0,02792	0,02853	0,02913	0,02974	0,22316	0,49657
IV	0,00769	0,00954	0,00898	0,00918	0,00948	0,00979	0,01003	0,01032	0,01060	0,01087	0,01115	0,01143	0,01162	0,01178	0,01207	0,01234	0,01261	0,01289	0,01316	0,01344	0,09647	0,21896
Death	0,54428	0,56969	0,58482	0,60301	0,62122	0,63943	0,65764	0,67585	0,69406	0,71227	0,73049	0,74870	0,76530	0,78346	0,80163	0,81969	0,83786	0,85603	0,87420	0,89237	6,30229	14,41201

Table n. 23.6: BC Stage Probability Matrix: Current Therapy - **Hospital Perspective** (Summary). Source: Own production.

≥ 65 years Female Gender HER+/ER-
Previous History of One Complication

	Cycles																				Acumul Total 5years	Acumul Total 10years
BC Stages	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20		
0	0,00003	0,00003	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00036	0,00075
I	0,00755	0,00721	0,00748	0,00771	0,00821	0,00844	0,00880	0,00903	0,00928	0,00952	0,00976	0,01001	0,01025	0,01049	0,01074	0,01098	0,01122	0,01147	0,01171	0,01195	0,08323	0,19181
II	0,01891	0,01783	0,01851	0,01907	0,02039	0,02095	0,02189	0,02248	0,02309	0,02369	0,02430	0,02490	0,02551	0,02611	0,02672	0,02732	0,02793	0,02853	0,02914	0,02974	0,20681	0,47701
III	0,00557	0,00729	0,00717	0,00746	0,00703	0,00735	0,00725	0,00749	0,00769	0,00789	0,00809	0,00830	0,00850	0,00870	0,00890	0,00910	0,00931	0,00951	0,00971	0,00991	0,07220	0,16223
IV	0,00256	0,00318	0,00350	0,00354	0,00312	0,00337	0,00330	0,00338	0,00347	0,00357	0,00366	0,00375	0,00384	0,00393	0,00402	0,00411	0,00420	0,00430	0,00439	0,00448	0,03298	0,07365
Death	1,23820	1,29600	1,33890	1,38062	1,41384	1,45522	1,49295	1,53427	1,57561	1,61695	1,65828	1,69962	1,74096	1,78230	1,82364	1,86498	1,90632	1,94765	1,98899	2,03033	14,34255	32,78562

Table n. 23.7: BC Stage Probability Matrix: Current Therapy - **Hospital Perspective** (Summary). Source: Own production.

≥ 65 years Female Gender HER-/ER+
Previous History of One Complication

	Cycles																				Acumul Total 5years	Acumul Total 10years
BC Stages	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20		
0	0,00010	0,00010	0,00011	0,00011	0,00011	0,00011	0,00011	0,00011	0,00011	0,00011	0,00011	0,00011	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00108	0,00226
I	0,02264	0,02164	0,02308	0,02376	0,02448	0,02520	0,02591	0,02663	0,02735	0,02806	0,05142	0,02838	0,03080	0,03148	0,03221	0,03294	0,03367	0,03440	0,03513	0,03586	0,24877	0,59507
II	0,05672	0,05349	0,05740	0,06470	0,06040	0,06265	0,06439	0,06617	0,06795	0,06973	0,07151	0,07441	0,07649	0,07834	0,08015	0,08197	0,08378	0,08560	0,08741	0,08923	0,62360	1,43249
III	0,01672	0,02188	0,02051	0,02146	0,02252	0,02266	0,02338	0,02403	0,02468	0,02533	0,02598	0,02663	0,02537	0,02611	0,02671	0,02731	0,02792	0,02853	0,02913	0,02974	0,22316	0,49657
IV	0,00769	0,00954	0,00898	0,00918	0,00948	0,00979	0,01003	0,01032	0,01060	0,01087	0,01115	0,01143	0,01162	0,01178	0,01207	0,01234	0,01261	0,01289	0,01316	0,01344	0,09647	0,21896
Death	3,71459	3,88799	3,99125	4,11537	4,23966	4,36394	4,48823	4,61251	4,73679	4,86108	4,98536	5,10964	5,22294	5,34690	5,47092	5,59418	5,71817	5,84217	5,96617	6,09017	43,01141	98,35803

Table n. 23.8: BC Stage Probability Matrix: Current Therapy - **Hospital Perspective** (Summary). Source: Own production.

24-64 years Female Gender HER+/ER-
Previous History of Two Complications

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00030	0,00062
I	0,00629	0,00309	0,00500	0,00415	0,00585	0,00553	0,00619	0,00623	0,00643	0,00659	0,00676	0,00693	0,00710	0,00726	0,00743	0,00760	0,00777	0,00793	0,00810	0,00827	0,05536	0,13050
II	0,01577	0,00707	0,01268	0,00962	0,01477	0,01348	0,01543	0,01542	0,01596	0,01634	0,01676	0,01718	0,01759	0,01801	0,01842	0,01884	0,01926	0,01967	0,02009	0,02050	0,13653	0,32285
III	0,00465	0,01363	0,00000	0,01627	0,00187	0,01124	0,00616	0,00894	0,00804	0,00873	0,00876	0,00905	0,00924	0,00947	0,00969	0,00991	0,01013	0,01035	0,01057	0,01079	0,07952	0,17750
IV	0,00214	0,00500	0,01196	0,00000	0,01114	0,00000	0,00714	0,00224	0,00523	0,00382	0,00469	0,00444	0,00472	0,00476	0,00490	0,00500	0,00512	0,00522	0,00534	0,00545	0,04867	0,09830
Death	0,15130	0,15836	0,16360	0,16870	0,17276	0,17782	0,18243	0,18748	0,19253	0,19758	0,20263	0,20768	0,21273	0,21778	0,22284	0,22789	0,23294	0,23799	0,24304	0,24809	1,75256	4,00618

Table n. 23.9: BC Stage Probability Matrix: Current Therapy - **Hospital Perspective** (Summary). Source: Own production.

24-64 years Female Gender HER-/ER+
Previous History of Two Complications

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00009	0,00009	0,00009	0,00009	0,00009	0,00009	0,00009	0,00009	0,00009	0,00009	0,00009	0,00009	0,00009	0,00010	0,00010	0,00010	0,00010	0,00010	0,00010	0,00010	0,00090	0,00186
I	0,01888	0,00927	0,01695	0,01492	0,01625	0,01642	0,01699	0,01742	0,01790	0,01836	0,03771	0,01277	0,02326	0,02130	0,02241	0,02277	0,02331	0,02380	0,02430	0,02481	0,16335	0,39979
II	0,04730	0,02121	0,04308	0,04112	0,03825	0,04171	0,04162	0,04343	0,04424	0,04557	0,04664	0,05436	0,04978	0,05559	0,05459	0,05679	0,05766	0,05905	0,06024	0,06151	0,40752	0,96375
III	0,01395	0,04089	0,01133	0,03288	0,02493	0,02671	0,02828	0,02816	0,02957	0,02995	0,03094	0,03160	0,02707	0,02760	0,02994	0,02916	0,03071	0,03090	0,03179	0,03234	0,26666	0,56872
IV	0,00641	0,01499	0,01523	0,00515	0,01664	0,00974	0,01319	0,01263	0,01302	0,01357	0,01370	0,01421	0,01550	0,01351	0,01468	0,01533	0,01500	0,01593	0,01586	0,01643	0,12057	0,27071
Death	0,45390	0,47509	0,49044	0,50572	0,52099	0,53327	0,54843	0,56362	0,57880	0,59399	0,60918	0,62436	0,63821	0,65335	0,66851	0,68357	0,69872	0,71387	0,72903	0,74418	5,26424	12,02722

Table n. 23.10: BC Stage Probability Matrix: Current Therapy - **Hospital Perspective** (Summary). Source: Own production.

≥ 65 years Female Gender HER+/ER-
Previous History of Two Complications

	Cycles																				Acumul Total 5years	Acumul Total 10years
BC Stages	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20		
0	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00030	0,00062
I	0,00629	0,00309	0,00500	0,00415	0,00585	0,00553	0,00619	0,00623	0,00643	0,00659	0,00676	0,00693	0,00710	0,00726	0,00743	0,00760	0,00777	0,00793	0,00810	0,00827	0,05536	0,13050
II	0,01577	0,00707	0,01268	0,00962	0,01477	0,01348	0,01543	0,01542	0,01596	0,01634	0,01676	0,01718	0,01759	0,01801	0,01842	0,01884	0,01926	0,01967	0,02009	0,02050	0,13653	0,32285
III	0,00465	0,01363	0,00000	0,01627	0,00187	0,01124	0,00616	0,00894	0,00804	0,00873	0,00876	0,00905	0,00924	0,00947	0,00969	0,00991	0,01013	0,01035	0,01057	0,01079	0,07952	0,17750
IV	0,00214	0,00500	0,01196	0,00000	0,01128	0,00000	0,00716	0,00224	0,00523	0,00382	0,00469	0,00444	0,00472	0,00476	0,00490	0,00500	0,00512	0,00522	0,00534	0,00545	0,04883	0,09846
Death	1,03258	1,08078	1,11656	1,15135	1,17905	1,21356	1,24502	1,27948	1,31395	1,34843	1,38290	1,41738	1,45185	1,48632	1,52080	1,55527	1,58974	1,62422	1,65869	1,69316	11,96075	27,34108

Table n. 23.11: BC Stage Probability Matrix: Current Therapy - **Hospital Perspective** (Summary). Source: Own production.

≥ 65 years Female Gender HER-/ER+
Previous History of Two Complications

	Cycles																				Acumul Total 5years	Acumul Total 10years
BC Stages	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20		
0	0,00009	0,00009	0,00009	0,00009	0,00009	0,00009	0,00009	0,00009	0,00009	0,00009	0,00009	0,00009	0,00009	0,00010	0,00010	0,00010	0,00010	0,00010	0,00010	0,00010	0,00090	0,00186
I	0,01888	0,00927	0,01695	0,01492	0,01625	0,01642	0,01699	0,01742	0,01790	0,01836	0,01883	0,01929	0,02165	0,02170	0,02231	0,02279	0,02330	0,02380	0,02430	0,02481	0,16335	0,38614
II	0,04730	0,02121	0,04308	0,03641	0,04060	0,04054	0,04220	0,04314	0,04439	0,04550	0,04668	0,04782	0,05374	0,05377	0,05534	0,05650	0,05777	0,05901	0,06026	0,06151	0,40436	0,95675
III	0,01395	0,04089	0,01133	0,03288	0,02259	0,02869	0,02702	0,02889	0,02917	0,03016	0,03084	0,03165	0,02470	0,02991	0,02842	0,03001	0,03029	0,03110	0,03170	0,03238	0,26557	0,56656
IV	0,00641	0,01499	0,01523	0,00515	0,01664	0,00893	0,01418	0,01182	0,01358	0,01322	0,01391	0,01409	0,01556	0,01259	0,01590	0,01429	0,01572	0,01549	0,01610	0,01631	0,12015	0,27010
Death	3,09773	3,24233	3,34713	3,45138	3,55563	3,63940	3,74289	3,84653	3,95018	4,05382	4,15747	4,26111	4,35560	4,45897	4,56239	4,66518	4,76858	4,87199	4,97540	5,07880	35,92702	82,08251

Table n. 23.12: BC Stage Probability Matrix: Current Therapy - **Hospital Perspective** (Summary). Source: Own production.

24-64 years Female Gender HER+/ER-
No previous History of Complications

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00003	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00018	0,00040
I	0,00645	0,00328	0,00318	0,00330	0,00349	0,00362	0,00372	0,00382	0,00393	0,00403	0,00413	0,00424	0,00434	0,00444	0,00454	0,00465	0,00475	0,00485	0,00496	0,00506	0,03882	0,08478
II	0,01615	0,00815	0,00782	0,00811	0,00863	0,00899	0,00924	0,00950	0,00975	0,01001	0,01026	0,01052	0,01077	0,01103	0,01129	0,01154	0,01180	0,01205	0,01231	0,01256	0,09635	0,21048
III	0,00476	0,00243	0,00307	0,00304	0,00291	0,00293	0,00302	0,00311	0,00319	0,00327	0,00336	0,00344	0,00352	0,00361	0,00369	0,00378	0,00386	0,00394	0,00403	0,00411	0,03174	0,06908
IV	0,00219	0,00114	0,00137	0,00146	0,00135	0,00134	0,00137	0,00141	0,00145	0,00149	0,00153	0,00156	0,00160	0,00164	0,00168	0,00172	0,00176	0,00179	0,00183	0,00187	0,01457	0,03156
Death	0,07735	0,03932	0,04085	0,04212	0,04327	0,04448	0,04575	0,04701	0,04828	0,04955	0,05081	0,05208	0,05335	0,05461	0,05588	0,05715	0,05841	0,05968	0,06094	0,06221	0,47797	1,04309

Table n. 24.1: BC Stage Probability Matrix: Current Therapy - **NHS Perspective** (Summary). Source: Own production.

24-64 years Female Gender HER-/ER+
No previous History of Complications

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00009	0,00005	0,00005	0,00005	0,00005	0,00005	0,00005	0,00005	0,00006	0,00006	0,00006	0,00006	0,00006	0,00006	0,00006	0,00007	0,00007	0,00007	0,00007	0,00007	0,00055	0,00119
I	0,01935	0,00984	0,00977	0,01009	0,01040	0,01070	0,01101	0,01131	0,01161	0,01192	0,01222	0,01253	0,01302	0,01333	0,01363	0,01394	0,01425	0,01456	0,01487	0,01518	0,11600	0,25354
II	0,04846	0,02445	0,02419	0,02500	0,02575	0,02651	0,02726	0,02801	0,02877	0,02952	0,03027	0,03103	0,03234	0,03309	0,03386	0,03462	0,03539	0,03616	0,03692	0,03769	0,28793	0,62930
III	0,01429	0,00729	0,00869	0,00883	0,00911	0,00937	0,00964	0,00991	0,01018	0,01044	0,01071	0,01098	0,01052	0,01083	0,01108	0,01133	0,01158	0,01183	0,01208	0,01233	0,09775	0,21102
IV	0,00657	0,00342	0,00366	0,00383	0,00393	0,00405	0,00416	0,00536	0,00433	0,00452	0,00463	0,00474	0,00484	0,00492	0,00504	0,00515	0,00527	0,00538	0,00550	0,00561	0,04382	0,09490
Death	0,23206	0,11796	0,12213	0,12594	0,12974	0,13354	0,13734	0,14115	0,14495	0,14875	0,15256	0,15636	0,16002	0,16382	0,16762	0,17141	0,17521	0,17901	0,18281	0,18661	1,43356	3,12899

Table n. 24.2: BC Stage Probability Matrix: Current Therapy - **NHS Perspective** (Summary). Source: Own production.

≥ 65 years Female Gender HER+/ER-
No previous History of Complications

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00006	0,00014
I	0,00117	0,00120	0,00117	0,00121	0,00128	0,00133	0,00137	0,00140	0,00144	0,00148	0,00152	0,00156	0,00159	0,00163	0,00167	0,00171	0,00175	0,00178	0,00182	0,00186	0,01306	0,02994
II	0,00292	0,00299	0,00287	0,00298	0,00317	0,00330	0,00339	0,00349	0,00358	0,00368	0,00377	0,00386	0,00396	0,00405	0,00415	0,00414	0,00414	0,00444	0,00452	0,00462	0,03238	0,07403
III	0,00086	0,00089	0,00113	0,00112	0,00107	0,00108	0,00111	0,00114	0,00117	0,00120	0,00123	0,00126	0,00129	0,00133	0,00136	0,00139	0,00141	0,00144	0,00148	0,00151	0,01077	0,02448
IV	0,00040	0,00042	0,00050	0,00054	0,00050	0,00049	0,00050	0,00052	0,00053	0,00055	0,00056	0,00057	0,00059	0,00060	0,00062	0,00063	0,00064	0,00066	0,00067	0,00069	0,00495	0,01118
Death	0,09542	0,09859	0,10242	0,10561	0,10848	0,11152	0,11470	0,11787	0,12105	0,12422	0,12740	0,13057	0,13375	0,13693	0,14010	0,14328	0,14645	0,14963	0,15280	0,15598	1,09988	2,51677

Table n. 24.3: BC Stage Probability Matrix: Current Therapy - **NHS Perspective** (Summary). Source: Own production.

≥ 65 years Female Gender HER-/ER+
No previous History of Complications

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00003	0,00003	0,00003	0,00018	0,00042
I	0,00350	0,00361	0,00359	0,00371	0,00382	0,00393	0,00404	0,00416	0,00427	0,00438	0,00449	0,00460	0,00478	0,00490	0,00501	0,00512	0,00524	0,00535	0,00546	0,00558	0,03901	0,08953
II	0,00876	0,00898	0,00889	0,00918	0,00946	0,00974	0,01001	0,01029	0,01057	0,01085	0,01112	0,01140	0,01188	0,01216	0,01244	0,01272	0,01300	0,01328	0,01356	0,01385	0,09673	0,22214
III	0,00258	0,00268	0,00319	0,00324	0,00335	0,00344	0,00354	0,00364	0,00374	0,00384	0,00394	0,00403	0,00386	0,00398	0,00407	0,00416	0,00425	0,00435	0,00444	0,00453	0,03324	0,07486
IV	0,00119	0,00126	0,00134	0,00141	0,00144	0,00149	0,00153	0,00157	0,00162	0,00166	0,00170	0,00174	0,00178	0,00181	0,00185	0,00189	0,00193	0,00198	0,00202	0,00206	0,01450	0,03326
Death	0,28626	0,29576	0,30622	0,31575	0,32529	0,33482	0,34436	0,35389	0,36342	0,37296	0,38249	0,39203	0,40120	0,41073	0,42025	0,42978	0,43930	0,44883	0,45835	0,46788	3,29873	7,54957

Table n. 24.4: BC Stage Probability Matrix: Current Therapy - **NHS Perspective** (Summary). Source: Own production.

24-64 years Female Gender HER+/ER-
Previous History of One Complication

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00009	0,00022
I	0,00179	0,00171	0,00177	0,00182	0,00194	0,00200	0,00208	0,00214	0,00220	0,00225	0,00231	0,00237	0,00243	0,00248	0,00254	0,00260	0,00266	0,00271	0,00277	0,00283	0,01970	0,04540
II	0,00447	0,00422	0,00438	0,00451	0,00483	0,00496	0,00518	0,00532	0,00546	0,00561	0,00575	0,00589	0,00604	0,00618	0,00632	0,00647	0,00661	0,00675	0,00690	0,00704	0,04895	0,11291
III	0,00132	0,00173	0,00170	0,00177	0,00166	0,00174	0,00172	0,00177	0,00182	0,00187	0,00192	0,00196	0,00201	0,00206	0,00211	0,00215	0,00220	0,00225	0,00230	0,00235	0,01709	0,03840
IV	0,00061	0,00075	0,00083	0,00084	0,00078	0,00079	0,00078	0,00080	0,00082	0,00084	0,00087	0,00089	0,00091	0,00093	0,00095	0,00097	0,00100	0,00102	0,00104	0,00106	0,00784	0,01747
Death	0,02143	0,02243	0,02317	0,02389	0,02447	0,02518	0,02584	0,02655	0,02727	0,02798	0,02870	0,02941	0,03013	0,03084	0,03156	0,03227	0,03299	0,03370	0,03442	0,03513	0,24819	0,56734

Table n. 24.5: BC Stage Probability Matrix: Current Therapy - **NHS Perspective** (Summary). Source: Own production.

24-64 years Female Gender HER-/ER+
Previous History of One Complication

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00002	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00004	0,00028	0,00065
I	0,00536	0,00512	0,00546	0,00562	0,00579	0,00596	0,00613	0,00630	0,00647	0,00664	0,00681	0,00698	0,00728	0,00745	0,00762	0,00780	0,00797	0,00814	0,00832	0,00849	0,05888	0,13575
II	0,01342	0,01266	0,01359	0,01398	0,01440	0,01482	0,01524	0,01566	0,01608	0,01651	0,01693	0,01735	0,01812	0,01854	0,01897	0,01940	0,01983	0,02026	0,02069	0,02112	0,14636	0,33758
III	0,00396	0,00518	0,00485	0,00508	0,00523	0,00538	0,00553	0,00569	0,00584	0,00599	0,00615	0,00630	0,00599	0,00618	0,00632	0,00646	0,00661	0,00675	0,00690	0,00704	0,05273	0,11743
IV	0,00182	0,00226	0,00212	0,00217	0,00224	0,00231	0,00238	0,00305	0,00246	0,00258	0,00264	0,00271	0,00275	0,00279	0,00286	0,00292	0,00299	0,00305	0,00312	0,00318	0,02339	0,05238
Death	0,06428	0,06728	0,06907	0,07122	0,07337	0,07552	0,07767	0,07982	0,08197	0,08412	0,08627	0,08842	0,09038	0,09253	0,09467	0,09681	0,09895	0,10110	0,10324	0,10539	0,74430	1,70205

Table n. 24.6: BC Stage Probability Matrix: Current Therapy - **NHS Perspective** (Summary). Source: Own production.

≥ 65 years Female Gender HER+/ER-
Previous History of One Complication

	Cycles																				Acumul Total 5years	Acumul Total 10years
BC Stages	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20		
0	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00003	0,00008
I	0,00066	0,00063	0,00065	0,00067	0,00071	0,00073	0,00076	0,00079	0,00081	0,00083	0,00085	0,00087	0,00089	0,00091	0,00093	0,00095	0,00098	0,00100	0,00102	0,00104	0,00724	0,01668
II	0,00164	0,00155	0,00161	0,00166	0,00177	0,00182	0,00190	0,00195	0,00201	0,00206	0,00211	0,00217	0,00222	0,00227	0,00232	0,00238	0,00243	0,00248	0,00253	0,00259	0,01798	0,04148
III	0,00048	0,00063	0,00062	0,00065	0,00061	0,00064	0,00063	0,00065	0,00067	0,00069	0,00070	0,00072	0,00074	0,00076	0,00077	0,00079	0,00081	0,00083	0,00084	0,00086	0,00628	0,01411
IV	0,00022	0,00028	0,00030	0,00031	0,00029	0,00029	0,00029	0,00029	0,00030	0,00031	0,00032	0,00033	0,00033	0,00034	0,00035	0,00036	0,00037	0,00037	0,00038	0,00039	0,00288	0,00642
Death	0,05485	0,05624	0,05809	0,05990	0,06134	0,06314	0,06477	0,06657	0,06836	0,07015	0,07195	0,07374	0,07554	0,07733	0,07912	0,08092	0,08271	0,08450	0,08630	0,08809	0,62342	1,42361

Table n. 24.7: BC Stage Probability Matrix: Current Therapy - **NHS Perspective** (Summary). Source: Own production.

≥ 65 years Female Gender HER-/ER+
Previous History of One Complication

	Cycles																				Acumul Total 5years	Acumul Total 10years
BC Stages	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20		
0	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00010	0,00024
I	0,00197	0,00188	0,00201	0,00207	0,00213	0,00219	0,00225	0,00232	0,00238	0,00244	0,00250	0,00256	0,00268	0,00274	0,00280	0,00286	0,00293	0,00299	0,00305	0,00312	0,02163	0,04987
II	0,00493	0,00465	0,00499	0,00513	0,00529	0,00544	0,00560	0,00575	0,00591	0,00606	0,00622	0,00637	0,00666	0,00681	0,00697	0,00713	0,00729	0,00744	0,00760	0,00776	0,05377	0,12402
III	0,00145	0,00190	0,00178	0,00187	0,00192	0,00198	0,00203	0,00209	0,00215	0,00220	0,00226	0,00232	0,00220	0,00227	0,00232	0,00238	0,00243	0,00248	0,00253	0,00259	0,01937	0,04314
IV	0,00067	0,00083	0,00078	0,00080	0,00082	0,00085	0,00087	0,00090	0,00092	0,00095	0,00097	0,00099	0,00101	0,00102	0,00105	0,00107	0,00110	0,00112	0,00114	0,00117	0,00839	0,01904
Death	0,16116	0,16869	0,17317	0,17855	0,18395	0,18934	0,19473	0,20012	0,20552	0,21091	0,21630	0,22169	0,22661	0,23199	0,23737	0,24271	0,24809	0,25347	0,25885	0,26423	1,86614	4,26746

Table n. 24.8: BC Stage Probability Matrix: Current Therapy - **NHS Perspective** (Summary). Source: Own production.

24-64 years Female Gender HER+/ER-
Previous History of Two Complications

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00008	0,00018
I	0,00179	0,00073	0,00118	0,00098	0,00138	0,00131	0,00146	0,00148	0,00152	0,00156	0,00160	0,00164	0,00168	0,00172	0,00176	0,00180	0,00184	0,00188	0,00192	0,00196	0,01340	0,03119
II	0,00447	0,00167	0,00300	0,00228	0,00350	0,00319	0,00365	0,00365	0,00378	0,00387	0,00397	0,00407	0,00416	0,00426	0,00436	0,00446	0,00456	0,00466	0,00475	0,00485	0,03306	0,07716
III	0,00132	0,00323	0,00000	0,00385	0,00044	0,00266	0,00146	0,00212	0,00190	0,00207	0,00207	0,00214	0,00219	0,00224	0,00229	0,00235	0,00240	0,00245	0,00250	0,00255	0,01904	0,04223
IV	0,00061	0,00118	0,00283	0,00000	0,00267	0,00000	0,00169	0,00053	0,00124	0,00090	0,00111	0,00105	0,00112	0,00113	0,00116	0,00118	0,00121	0,00124	0,00126	0,00129	0,01166	0,02340
Death	0,02143	0,01870	0,01932	0,01992	0,02040	0,02100	0,02154	0,02214	0,02274	0,02333	0,02393	0,02453	0,02512	0,02572	0,02632	0,02691	0,02751	0,02811	0,02870	0,02930	0,21053	0,47669

Table n. 24.9: BC Stage Probability Matrix: Current Therapy - **NHS Perspective** (Summary). Source: Own production.

24-64 years Female Gender HER-/ER+
Previous History of Two Complications

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00002	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00003	0,00024	0,00054
I	0,00536	0,00219	0,00401	0,00353	0,00385	0,00389	0,00402	0,00412	0,00424	0,00435	0,00446	0,00457	0,00513	0,00514	0,00528	0,00539	0,00552	0,00563	0,00575	0,00587	0,03956	0,09229
II	0,01342	0,00502	0,01020	0,00862	0,00961	0,00960	0,00999	0,01021	0,01051	0,01077	0,01105	0,01132	0,01272	0,01273	0,01310	0,01337	0,01367	0,01397	0,01426	0,01456	0,09794	0,22869
III	0,00396	0,00968	0,00268	0,00778	0,00535	0,00679	0,00640	0,00684	0,00691	0,00714	0,00730	0,00749	0,00585	0,00708	0,00673	0,00710	0,00717	0,00736	0,00750	0,00767	0,06352	0,13476
IV	0,00182	0,00355	0,00361	0,00122	0,00394	0,00211	0,00336	0,00330	0,00302	0,00320	0,00326	0,00335	0,00368	0,00298	0,00376	0,00338	0,00372	0,00367	0,00381	0,00386	0,02913	0,06460
Death	0,06428	0,05611	0,05792	0,05972	0,06153	0,06298	0,06477	0,06656	0,06836	0,07015	0,07194	0,07374	0,07537	0,07716	0,07895	0,08073	0,08252	0,08431	0,08610	0,08789	0,63238	1,43108

Table n. 24.10: BC Stage Probability Matrix: Current Therapy - **NHS Perspective** (Summary). Source: Own production.

≥ 65 years Female Gender HER+/ER-
Previous History of Two Complications

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00000	0,00003	0,00007
I	0,00055	0,00027	0,00043	0,00036	0,00051	0,00048	0,00054	0,00054	0,00056	0,00057	0,00059	0,00060	0,00062	0,00063	0,00065	0,00066	0,00068	0,00069	0,00070	0,00072	0,00481	0,01135
II	0,00137	0,00061	0,00110	0,00084	0,00128	0,00117	0,00134	0,00134	0,00139	0,00142	0,00146	0,00149	0,00153	0,00157	0,00160	0,00164	0,00167	0,00171	0,00175	0,00178	0,01187	0,02807
III	0,00040	0,00119	0,00000	0,00141	0,00016	0,00098	0,00054	0,00078	0,00070	0,00076	0,00076	0,00079	0,00080	0,00082	0,00084	0,00086	0,00088	0,00090	0,00092	0,00094	0,00692	0,01543
IV	0,00019	0,00043	0,00104	0,00000	0,00098	0,00000	0,00062	0,00019	0,00045	0,00033	0,00041	0,00039	0,00041	0,00041	0,00043	0,00043	0,00044	0,00045	0,00046	0,00047	0,00425	0,00856
Death	0,04480	0,04689	0,04844	0,04995	0,05116	0,05265	0,05402	0,05551	0,05701	0,05850	0,06000	0,06150	0,06299	0,06449	0,06598	0,06748	0,06897	0,07047	0,07197	0,07346	0,51894	1,18625

Table n. 24.11: BC Stage Probability Matrix: Current Therapy - **NHS Perspective** (Summary). Source: Own production.

≥ 65 years Female Gender HER-/ER+
Previous History of Two Complications

BC Stages	Cycles 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Acumul Total 5years	Acumul Total 10years
0	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00001	0,00009	0,00020
I	0,00164	0,00081	0,00147	0,00130	0,00141	0,00143	0,00148	0,00151	0,00156	0,00160	0,00164	0,00168	0,00188	0,00189	0,00194	0,00198	0,00203	0,00207	0,00211	0,00216	0,01421	0,03358
II	0,00411	0,00184	0,00375	0,00317	0,00353	0,00353	0,00367	0,00375	0,00386	0,00396	0,00406	0,00416	0,00467	0,00468	0,00481	0,00491	0,00502	0,00513	0,00524	0,00535	0,03516	0,08320
III	0,00121	0,00356	0,00099	0,00286	0,00196	0,00249	0,00235	0,00251	0,00254	0,00262	0,00268	0,00275	0,00215	0,00260	0,00247	0,00261	0,00263	0,00270	0,00276	0,00282	0,02309	0,04927
IV	0,00056	0,00130	0,00132	0,00045	0,00145	0,00078	0,00123	0,00103	0,00118	0,00115	0,00121	0,00123	0,00135	0,00109	0,00138	0,00124	0,00137	0,00135	0,00140	0,00142	0,01045	0,02349
Death	0,13440	0,14068	0,14522	0,14975	0,15427	0,15790	0,16239	0,16689	0,17139	0,17588	0,18038	0,18488	0,18898	0,19346	0,19795	0,20241	0,20689	0,21138	0,21587	0,22035	1,55877	3,56131

Table n. 24.12: BC Stage Probability Matrix: Current Therapy - **NHS Perspective** (Summary). Source: Own production.

These tables are just the summary of the 80 Semi-Markov Matrix construct that comprise the model from each perspective, presented in detail in **Appendix 8, Appendix 9 and Appendix 10**, from the perspectives of the Oncologist (also referred as the clinical or the physician perspectives), the Hospital and the NHS, respectively.

Each matrix represents a Markov cycle, from three different previous disease complication odds (0,1 and 2), two age groups (24-64 and +65) and two tumor types (HER-2+/ER- and HER-2-/ER+), which have different incidence rates, as previously described.

When analyzing the model in detail, it is important to know how the tables were done, so its timely to present a brief explanation for further reproduction:

At the first column are presented the *six health stages* considered; at the second column, can be found the *population disease odds (PDO)* at each disease stage; moving to the right, can be found the metastasis incidence average per disease stage and corresponding metastasis population odds (calculated by the product of the second column with this one); then, the previous history of acute renal failure per disease stage, and corresponding acute renal failure population odds; the previous history of acute hepatic failure per disease stage, and corresponding acute hepatic failure population odds; and the same for acute pulmonary disease, acute cardiovascular event, acute arthralgia, osteoporosis, acute cytopenia and acute diarrhea; the ending column represents the *weighted total cycle complication odds per cycle and BC stage (PTCCO)*.

The *metastasis average per BC disease stage* was calculated, based on the following (previously identified and presented) values:

Stage	**Tumor size**	**Lynphatic nodes affected**	Metastasis	Metastasis average
0	-	-	0,00	0,00
I	< 2cm	-	0,00	0,00
IIA	< 2cm	+	9,79	6,83
	2-5cm	-	0,42	
IIB	2-5cm	+	15,03	
	> 5cm	-	2,07	

IIIA	-	++	1,74	19,39
	≤ 5cm	++	15,03	
	> 5cm	++	20,26	
IIIB	Metastisation to other structures/ organs		20,26	
IIIC	Metastisation to other structures/ organs		20,26	
IV	Metastisation to other structures/ organs		20,26	20,26

Table n. 25: Metastasis average calculation:
Source: Own calculations.

On the other hand, *previous history of complications* were calculated as follows:
At the first line (stage 0 or cancer free after intervention) we indicated the complication incidence at the Portuguese population without BC (although despising the fact that these population had already the disease, and regarding that very few are BC cancer diagnosed at this stage); at the second line (stage I), we presented the complication probability in BC population (prior to chemotherapy, once we will consider the matrix catching the beginning of the cycle); at the third, fourth and fifth lines, the complication probability during/after chemotherapy (corresponding to stages II, III and IV); and at the last, we presented specific disease death rates.
Considering the complication probability during *or* after chemotherapy is dangerous, because we are not comparing comparable realities, despising accumulated toxic effects in a latter reality; however, we had no other chance, considering the data available. Other bias may emerge from the fact that, to differentiate the stage I complication probability (characterized by the absence of metastasis) from metastised stages, we considered that previous chemotherapy treatment had been done prior to surgery, or because cancer had progressed after previous cytostatic treatment. We hadn't contemplated, however, that women can be in these stages at the time of the diagnostic and that the cytostatic treatment administrated may not be adjuvant to surgery, because this procedure wasn´t adequate. Yet, this wasn´t the target of our model and though, is excluded from the preconditions imposed for the study development in this thesis, which considers exclusively systemic chemo-endocrine-immunotherapy after surgery and RT, this last procedure, if adequate (as described before).

However, as we are considering a six month cycle and all the incidence data collected was of a year horizon, we divided the values by two. Other point to remind is that for zero previous history of disease, the first line was zero (of course), as well as the first six month matrix therapy complication cycle (and not disease complication, represented by metastasis incidence).

The PTCCO value represents the sum of all complication odds at population and was weighted according to therapy adverse side effects of the precise drugs being administrated at the time of that cycle (according to IPOL previous presented most current protocols, considering the first matrix cycle alongside with the first treatment cycle). The assignment of weights to the model is necessary since adverse events complication probabilities are directly related to the toxicities of the drugs being administrated at that model cycle time.
If median toxicity, the previous correspondent disease complication odds were assigned the weight one; in case of higher toxicity were assigned the weight two and for no identified related toxicity, we assigned the weight 0,5.

As previously described when we presented the Markov model scheme, complications were assumed to last 9 weeks and imply the BC therapy interruption (while weakening the body), ticking one BC stage progression in the next Markov six month cycle. So, the PTCCO value identified in *health stage x* was decreased in the value of incidence of the correspondent *x health stage* in the next Markov cycle (semi-matrix) and the PTCCO value identified in *health stage x-1* was added to this value. Additional six month disease prevalence was also added to each heath stage every Markov cycle, meaning that *Death stage* integrated either BC incidence and prevalence related mortality rates (added per cycle) plus BC non-related mortality rate, incidence and prevalence (as previously proposed).

Note also that different female population age rates and different mortality rates (both BC related and not related) previously described, were accounted to the different age groups; different tumor type incidence (that correspond to different treatment protocols) and two complications probability calculations (results shown at the PTCCO of the respective column), were also integrated.

Were, however, identified three main **disadvantages of the matrix formation**. The first is the difficulty in performing matrix inversion, although this is today less of a problem than when Beck and Pauker described the technique (1993), because many commonly available microcomputer spreadsheet programs now perform matrix algebra. The second disadvantage is the need to represent all the possible ways of making a transition from one stage to another as a single transition probability.

Stahl (2008) identified other two main limitations of Markov Models: the first is that stage transitions can only occur at the end of a cycle, which can create some bias (that´s why is a good practice to incorporate a half-cycle correction in calculating utilities, no matter what the cycle length, which we haven´t considered); secondly, Markov cycle may force the analyst to simplify assumptions regarding transition probabilities (and we were forced to do it).

2.3.2.2.5.3.3.2. CUA DATA: MARKOV STAGES UTILITIES

When performing cost-utility analyses, a separate incremental utility may be specified for each stage. The model is evaluated separately for cost and survival. Female life expectancy is described in the next tables, although considering different age groups of ours.

Female Life Expectancy	
At Birth (Years)	82,43
At 45 years old (Years)	38,59
At 65 Years old (Years)	20,35

Table n. 26: Female Life Expectancy data in Portugal, 2009
Source: Portuguese Statistics, Health Statistics 2002 -2009 (Carrilho, 2009)

	Age at Diagnosis					
	<50	50–59	60–69	70–79	80+	All
Life expectancy at diagnosis						
Stage I	26.6	21.1	15.7	10.9	6.3	16.9
Stage II	21.9	17.4	13.4	9.6	5.5	14.2
Stage III	10.4	9.2	8.0	6.4	4.1	7.9
Stage IV	3.9	3.4	3.3	2.9	2.1	3.1
All	21.9	18.0	13.8	9.8	5.6	14.5

Table n. 27: Life expectancy according to age and BC progression stages.
Source: Berkowitz, Gupta and Silberman (2000)

Note that from table n. 27, we can assume that life expectancy at BC diagnosis varies greatly with disease stage at this time and with age. Although this table is more detailed, we opted to consider the first (table n.26) to our model data processor, since this data were from the Portuguese population and assumed to be values that can be compared more precisely with the age groups chosen to built the BC model.

The measurement and valuation of clinical effects is a significant component of economic evaluation. Decision makers are commonly interested in how a particular health intervention works in everyday practice (Teerawattananon, 2008).
Over the years, most quality-of-life research and its evaluation in patients with BC was focused on palliative and adjuvant therapy. In palliative therapy, because the objective of the treatment is not curative and the patient's well being is of paramount importance. In the adjuvant setting, where cure may be achieved, the trade-off between the potential toxicity of a given treatment and the possible benefit of prolonged survival is equally important. The quality of the survival itself is important for patients and, in this respect, the *Quality-Adjusted Time Without Symptoms and Toxicity (Q - TWiST)* method was found an important application (Radice & Redaelli, 2003), although not explored in this thesis.

The wide consensus of investigators agrees to measure four key components of quality of life: *physical, emotional, social functioning and symptoms*. There is less agreement about which specific measures should be used by investigators assessing these components. Again, consensus has been consolidating in recent years about the concept that patient-reported outcomes should supplement physician judgments of treatment-related toxic effects, routinely reported in most trials (Radice & Redaelli, 2003).

The concept of quality of life has evolved in response to these concerns, and many types of HR-QOL questionnaires have been developed. These are sometimes disease-oriented and other times dimension-specific.

- Disease-oriented HR-QOL instruments for cancer include the *Cancer Rehabilitation Evaluation System (CARES), the Functional Living Index for Cancer (FLIC), the 30-item European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) and the Functional Assessment of Cancer Therapy-General (FACT-G);*
- Dimension-specific HR-QOL instruments include the *Symptom Distress Scale (SDS) and the Rotterdam Symptom Checklist (RSCL).*
- A questionnaire developed specifically for BC is the *Breast Cancer Chemotherapy Questionnaire (BCQ).*

Of the above questionnaires, the BCQ is applicable only to breast cancer, while the others can also be used for other types of cancer. In addition, the BCQ is highly specialized for adjuvant chemotherapy with an emphasis on physical toxicity (Radice & Redaelli, 2003).

As the number of long-term survivors of cancer continues to grow, the medical community is becoming more concerned about issues of survivor and quality of life.

When included in clinical trials, HR-QOL questionnaires are aimed to detect differences (if any) among treatment groups. The major determinants in any HR-QOL questionnaire are usually related to the adverse events associated with the treatment. Therefore, if experimental treatments are not very different in this respect, it is likely that no HR-QOL difference among treatments will be found.

In cost-effectiveness studies, the consequences must be measured keeping in mind that what you want to evaluate is, ultimately, the contribution of each alternative to improve patients health. Thus, the endpoints to be considered should be referring to the impact of therapeutic strategies on the duration of life.

However, given the difficulty of quantifying this impact, indicators such as the reduction in length of disability or the improvement of clinical parameters, although not directly linked with life extension, may be adopted (Silva *et al.*, 1998).

In cost-utility studies, years of life are weighted by the quality of life, which can be measured using various instruments. Some measure the different levels of activity limitations on a cardinal scale between 0 and 1 (like the methods of *standard gamble*, *time trade-off* and the *EQ-5D*, for example), where 0 represents death and 1, the stage of perfect health, while others are merely descriptive of such levels of restraint (the *SF-36*). It is possible to adopt any of these to our country if previously validated in it, and considered appropriate to the study.

In all cases, it is advisable to consider at least one reference group (knowledgeable about the disease) qualified to contribute with their opinion to correct the values determined in the responses of patients, in order to obtain weights reflecting the society opinion about the quality of life that corresponds to each level of activity limitation.

In the case of the descriptive tools, it is advised that, whenever possible, are simultaneously presented results based on generic measures (such as the *SF-36*, *Sickness Impact Profile and Nottingham Health Profile*) and specific tools (to measure concrete health problems) (Silva *et al*., 1998).

In healthcare, **utilities are** a measure of the patients preferences for health stages. A summary of the utilities associated to BC health stages were obtained from the literature and is presented in the next table.

Utilities are unique to the health stages, regardless of the treatment (Brown, Lipscomb & Snyder, 2001)**.** As the patients in the model experience the different health stages, the utilities increase or decrease as appropriate:

BC Stage	Utility	Source
Stage 0	**0,97**	Liberato, Marchetti & Barori (2007)
Stage I	**0,84**	Brown, Hutton & Burrell (2001); Martin, Gagnon, Zhang, Bokemeyer, Koody & Hout (2003)
Stage II	**0,64**	Brown, Hutton & Burrell (2001); Martin *et al.* (2003)
Stage III	**0,61**	Dranitsaris *et al.* (2009); Dedes *et al.* (2009)
Stage III	0,62	Brown, Hutton & Burrell (2001); Martin *et al.* (2003)
Stage IV	**0,26**	Dranitsaris *et al.* (2009); Dedes *et al.* (2009)
Stage IV	0,23	Brown, Hutton & Burrell (2001); Martin *et al.* (2003)
Death	**0,00**	Brown, Hutton & Burrell (2001); Martin *et al.* (2003)

Table n. 28: BC stage Utilities.

Source: Own construct.

2.3.2.2.5.3.3.3. CUA DATA: MARKOV STAGES DIRECT COSTS

Costs are the product of goods and services consumed and the valuation (prices) applied to those resources (Ramsey, McIntosh & Sullivan, 2001). This means that identify costs is to enumerate all relevant resources consumed due to the adoption of each alternative therapy, in order to enable their subsequent measurement and valuation (Silva *et al*., 1998). To this end, we must first specify the probability of all events and clinical options that involve the consumption of resources. Thereafter, the relevant events should be selected according to the perspective of the analysis, previously defined.

If the analysis is done on a **societal perspective**, the relevant costs are global and supported by all the actors in society. In this context, transfers of income (for example, sickness or unemployment allowances) should not be considered since, in these cases, there is a gain for some individuals and a loss in the same amount, for others, not giving lead to any consumption but only a redistribution of resources.
All direct and indirect costs must be identified. It is also recommended the inclusion of intangible costs (pain felt by the patient through the use of invasive surgical techniques) although is recognized that due to difficulties in measurement, these are never quantified and valued (Silva *et al*.,1998).

Direct costs include medical and non-medical care costs:

- ✓ *Medical care costs* are due to treatment and its consequences, such as expenses associated with hospitalization or consultation; spending on diagnostic and therapeutic and nursing care and rehabilitation, or incurred by the death of the patient.
- ✓ *Non-medical costs* are those concerning the provision of informal services, as home nursing by family members and other services aimed to prevent or eliminate the risk of recurrence or occurrence of other diseases.
- ✓ *Other direct costs* relevant to society are associated with research activities, staff training, construction and facilities management undertaken by public or private services. Spending on health care, incurred by the fact that patients (because of treatment) see their life expectancy increased and, therefore, come to consume more health care in the future, is another example. We should also consider all the costs

related to patient and family transportation to the hospital, accommodation costs (if the patient has to move out of his area of residence), or maintenance costs of their housing (if the patient is constrained to hire someone to replace or assist in household chores).

For example, Radice & Redaelli (2003) presented the estimated direct costs of BC, as follows (focus on the age grouping, a lot more detailed than what we "were forced" to assume in the CHEAUL model, for the reasons presented):

Table n.29: Estimated total direct cost of breast cancer (stages III and IV) – 1995 values. Source: Decision Resources, Inc.
Source: Radice and Redaelli (2003)

Item	Total direct cost ($US; 1995 values)	
	Stage III	Stage IV
Physician visits	27 300 000	25 602 675
Mammography	4 285 809	1 866 125
Biopsy	4 018 560	7 607 652
Bone scan	669 760	1 267 942
Chest x-ray	384 210	1 394 105
CAT scan	1 839 368	5 133 956
Liver CT scan	2 899 224	5 488 604
MRI scan	4 096 225	15 434 799
Drug therapy	42 000 000	114 000 000
Mastectomy/other surgery	110 112 750	133 794 703
Radiotherapy	4 950 000	9 265 730
Bone marrow transplantation	NA	260 172 920
Hospice care	NA	84 651 000
Home healthcare	78 825 600	98 532 000
Total direct costs	**281 377 506**	**764 212 211**

CAT = computerized axial tomography; **CT** = computed tomography; **MRI** = magnetic resonance imaging; **NA** = not applicable.

Table n. 30: Cost ($US; 1992 values) for breast cancer by stage, age and co morbidity
Source: Radice and Redaelli (2003)

	Initial care			Continuing care			Terminal care		
	N	cost	SE	n	cost	SE	n	cost	SE
Total no. of patients	645	10 813	224	2111	1084	36	187	17 686	1399
Stage									
CIS	86	8 515	602	212	888	113	10	11 222	6054
Local	390	10 835	277	1309	958	45	74	14 962	2179
Regional	150	12 273	451	545	1423	70	74	20 323	2199
Distant	8			23	2921	388	22	20 610	4158
Unknown	11			22	1308	349	7	18 630	7759
Age (years)									
35–49	187	11 791	411	367	1078	89	20	28 196	4053
50–64	185	11 159	417	626	991	65	47	21 426	2684
65–79	225	10 054	373	903	1104	54	81	16 857	2041

≥80	48	9 135	797	215	1353	113	39	9 937	2945
Co morbidity									
Low	262	10 577	347	758	684	56	28	17 354	3575
Medium	175	10 712	425	673	1091	59	47	15 859	2818
High	94	11 053	590	559	1543	65	107	18 812	1861
a The number of patients with co morbidity does not match the total number of patients because when breast cancer is in early stages roughly 30% of patients do not have concomitant additional diseases. **CIS** = carcinoma *in situ*; **SE** = standard error.									

Remind that the total costs of initial care increase with stage at diagnosis, but do not change with co-morbidity.

Berkowitz, Gupta and Silberman (2000) also considered a more detailed age group, as presented below:

	Age Group					
	Under 50	50 to 59	60 to 69	70 to 79	80 and over	All
Number of cases	9,345	12,919	16,192	17,451	14,576	70,483
Cost ($/person-year)						
Hospital + professional fees	15,871	8,225	8,500	9,056	10,300	10,087
Radiotherapy	1,515	1,544	1,569	1,619	1,714	1,590
Chemotherapy	354	413	441	515	650	466
Hormonal therapy	44	168	181	204	236	168
Management and tests	2,254	1,913	1,951	2,028	2,212	2,049
Drug (excluding hormones)	1,788	1,729	1,724	1,714	1,701	1,731
Terminal care	3,387	2,926	3,064	3,336	3,720	3,244
Total	25,212	16,917	17,430	18,473	20,560	19,335

Table n. 31: Two-year undiscounted lifetime costs of care for metastatic breast cancer.

Source: Berkowitz, Gupta and Silberman (2000).

Regarding **indirect costs**, must be considered only those related to the loss of working productivity as a consequence of the disease. These costs should be calculated deducted from earnings (productivity gains resulting from the treatment). Note that these must always be reported separately and their impact on the results should be subjected to sensitivity analysis.

Radice & Redaelli (2003) also presented the estimated indirect costs of BC and cost comparison, as shown in the next tables:

Table n. 32: Estimated total indirect cost of breast cancer (stages III and stage IV) – 1995 values. Source: Radice and Redaelli (2003)		
Item	Estimated indirect costs ($US; 1995 values)	
	Stage III	Stage IV
Missed days of work (A)	2 727 002	310 750
Missed days of work due to mortality (B)	NA	5 166 500
Total (C = A + B)	2 727 002	5 477 250
Cost of a missed day of work (D) [$US]	111	111
Total indirect costs(C * D) [$US]	302 697 222	607 974 750
NA = not applicable.		

Note that combining the number of missed days from work with the incident population number, results in more than 2,7 million days of missed work…, indicating that indirect costs have a significant weight in Global BC costs. The next table is shows the proof.

Table n. 33: Direct and indirect cost ($US) of breast cancer per patient by stage – 1995 values. Source: Radice and Redaelli (2003)		
Cost	Stage III	Stage IV
Direct	3865	15 671
Indirect	4158	12 467
Total costs	**8024**	**28 138**

Finally, it should be noted that the objective is to compare two different alternatives so, only costs that are qualitatively different or that, being the same type, differ in quantitative terms in the different treatments, should be considered.

From the NHS, Hospital and Clinical perspectives, costs to attend are only direct costs (Silva, *et al.*, 1998), reason why we have only contemplated these.

The total cost of each alternative therapy should be obtained through the product of a vector whose elements are the quantities of resources consumed on average per case by the vector of its unit price (Silva *et al.*, 1998).
Thus, initially, we should quantify the resources used by each patient in physical units, such as, for example, the number of nursing hours required for treatment, the average length of stay and number of consultations, based on clinical experience nationwide.

Market unit prices are considered a privileged cost determination instrument. A possible alternative is the use of *shadow prices* associated with the resources consumption.

Although this method is preferable to the previous one, is vulnerable to certain subjectivity. One example is the use of GDHs values or of conventional tables as "approximations" to the price of care, in Portugal. These are based on the assumption that the NHS is the market regulator and therefore, fixed prices reflect the relationship between the amount of resources consumed and the social benefits obtained. However, to our study purpose, this was not the case.

The *Portuguese Patient Diagnosis Related Group Classification System is designated GDHs*. This is a classification system for acute episodes of illness treated in hospital, which allows defining operationally the hospital´s production. The GDHs are defined in terms of the following variables: primary diagnosis, surgical procedures associated diseases and complications (involving research, care, treatment and /or a stay), clinical procedures, sex of the patient and destination after discharge. The groups were designed to be consistent in terms of clinical and of resource consumption. It is assumed to exist a pattern of resources use, including hospital room, operating room, pharmacy, diagnostic aids and therapy, for each pathology and intervention (Article 3 - Ordinance 132/2009, 30 January – available in **Appendix N.11**).

Diagnostics, surgeries and other medical relevant acts are coded according to the *International Coding of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM). The table is based on the wrapper of GDH, All Patients DRG, version 21.0, developed in the U.S., whose corresponding version of ICD-9-CM is of 2004 (Article 3 - Ordinance 132/2009, 30 January – see **Appendix N.11**).

Since we will only consider the economical evaluation difference between two medicines/ systemic drug therapies, we need simply to attend the next GDHs, essential for assessment of associated patients costs:

Table n. 34: National Table of Primary and Secondary Diagnosis Related Groups:
Source: Ordinance 132/2009, 30 January

DRG 9 - Skin, Subcutaneous Tissue and **Breast diseases and disorders**	Price (€)	Relative Weight
GDH 274 - Malignancies of the breast, with CC	4.321,88	1,8036
GDH 275 - Malignancies of the breast, without CC	1.416,90	0,5913
GDH 410 - Chemotherapy:		

ICD-9-CM 00:10 chemotherapeutic agent Implant	-	-
ICD-9-CM 99.25 Injection or infusion of therapeutic substance-cancer chemotherapy	-	-
CD-9-CM 99.28 antineoplasic immunotherapy	-	-

We may also consider the following codes:

Table n. 35: Table of Complementary Diagnosis and Therapy: Source: Ordinance 132/2009, 30 January		
Administration of cytotoxic therapy, with the following codes:	Price (€)	Relative Weight
65001 Treatment of short duration (less than one hour)	-	-
65002 Treatment of medium duration (between one and three hours)	-	-
65003 Treatment of long-term (over 3 hours)	-	-

However, excluding interment, ambulatory GDH price only applies if procedures are performed in the operating room, which means that the cost of cytostatic therapy, administrated during a (few) hour(s), in ambulatory day care, weren´t accounted, as it is shown. We were though forced to use published literature costs (although regarded as not adapted to the Portuguese context), to fulfill our goal.

These values reflect considerations (administrative and budgetary implications) that have nothing to do with market mechanisms. Yet, they should be a privileged source of costs in the absence of a standard national table cost. If the desired value is not listed in the tables (as proven), valuation should be done using the valuation method most suited to each case.

Though, we decided to obtain the data through published literature and then to adequate/reevaluate it in the light of the national reality. For that, we investigated and applied our day's exchange rates, and adjusted the cost value considering the year of costing and an account rate year of 5 % (as discussed in the next chapter).

The results are shown bellow.

	Costs	**Euro convertion***	**Source**	**Year of costing**	**Account Rate/year**	**Accounted 2011 cost**
Cyclophosphamide[a] 500mg/m2 IV 6 month (850mg*6= 5100mg)	US$0,01/mg **US$51**	**37 €**	Mackey *et al.* (2009)	2007	5%	**43 €**
5-Flourouracilo[a] 500mg/m^2 IV 6 month (850mg*6= 5100mg)	US$0,01/mg **US$51**	**37 €**	Mackey *et al.* (2009)	2007	5%	**43 €**
Epirrubicin[a] 750mg/m^2 IV 6 month (1275mg*6=7650mg)	US$4,00/mg **US$30600**	**22.234 €**	Mackey *et al.* (2009)	2007	5%	**25.740 €**

Trastuzumab[b] 8mg/kg+6mg/Kg 12 month 520mg+390mg*11=4810mg)	US$6,14/mg **US$29533**	**21.459 €**	Mackey *et al.* (2009)	2007	5%	**24.842 €**
Tamoxifen 20mg/day po 1825days (20mg*1825=36500mg/5years)	€11,09/30cp 20mg; €0,02/mg = **€85,58**	**86 €**	Infarmed (2011)	2011	5%	**100 €**
Cyclophosphamide[a] 500mg/m^2 IV 6 month (850mg*6= 5100mg)	US$0,01/mg **US$51**	**37 €**	Mackey *et al.* (2009)	2007	5%	**43 €**
Docetaxel[b]75mg/m^2 6 month (75mg*6=450mg)	US$11,42/mg **US$5139**	**3.734 €**	Mackey *et al.* (2009)	2007	5%	**4.323 €**
Doxorubicin[a]50mg/m^2 6 month (85mg*6=510mg)	US$0,57/mg **US$290,7**	**211 €**	Mackey *et al.* (2009)	2007	5%	**245 €**
Letrozole 2,5mg/day 1825days (2,5*1825days=4562,5mg/5years)	€147,84 /30cp 20mg €0,25/mg = **€1140,6**	**1.141 €**	Infarmed (2011)	2011	5%	**1.141 €**
5-Flourouracilo200mg/m^2/day,7days per month (340*7*6=14280mg/ 6month)	US$0,01/mg **US$142,8**	**104 €**	Mackey *et al.* (2009)	2007	5%	**120 €**
Paclitaxel175mg/m^2 4 month (1105mg per cycle*4 drug cycles = 4420mg)	US$0,70/mg **US$3094**	**2.248 €**	Mackey *et al.* (2009)	2007	5%	**2.603 €**
Bevacizumab10mg/kg 12month (650mg per cycle *12 drug cycles = 7800mg)	€4,10/mg; **€ 31.880**	**31.880 €**	Dedes et al.(2009)	2008	5%	**35.149 €**
ARF event	US$29823	**21.669 €**	Bates *et al.*(2001)	2000	5%	**35.298 €**
AHF event	€ 56.219	**56.219 €**	Lock *et al.* (2009)	2008	5%	**61.983 €**
APD event	£6480	**7.576 €**	Plant *et al.* (2003)	2002	5%	**11.194 €**
ACVE event : Ischaemic cardiovascular or cerebrovascular disease	£4775	**5.583 €**	Mansel *et al.*(2007)	2003	5%	**7.856 €**
Ost - Hip fracture	£7398	**8.650 €**	Karnon *et al.* (2006)	2004	5%	**11.592 €**
AA event	US$274,8	**192 €**	Yelin *et al.* (2003)	2003	5%	**271 €**
AC event (febrile neutropenia+ anemia)	Can$9016	**6.685 €**	Dranitsaris *et al.* (2009)	2006	5%	**8.126 €**
AD event	Can$2649	**1.964 €**	Dranitsaris *et al.* (2009)	2006	5%	**2.388 €**
Drug Preparation and administration per drug cycle						
Drug Administration <1h[a]	Can$30	**22 €**	Dranitsaris *et al.* (2009)	2006	5%	**27 €**
Drug Administration 1-3h[b]	Can$121	**90 €**	Dranitsaris *et al.* (2009)	2006	5%	**109 €**
Drug Administration >3h[c]	Can$134	**99 €**	Dranitsaris *et al.* (2009)	2006	5%	**121 €**
Disease free (Stage 0 - routine follow up)	£70	**82 €**	Mansel *et al.*(2007)	2003	5%	**115 €**
High risk of recurrence/Beginning of recurrence (5 years of Stage I BC)					Total	**29.744€**
Year 1	£16824	**19.671 €**	Karnon *et al.* (2006)	2004	5%	**26.361 €**
Year 2	£622	**727 €**	Karnon *et al.* (2006)	2004	5%	**975 €**
Year 3	£380	**444 €**	Karnon *et al.* (2006)	2004	5%	**595 €**
Year 4	£668	**781 €**	Karnon *et al.* (2006)	2004	5%	**1.047 €**
Year 5	£489	**572 €**	Karnon *et al.* (2006)	2004	5%	**766 €**
Loco regional recurrence (5 years of Stage II BC)					Total	**26.842€**
Year 1	£12916	**15.101 €**	Karnon *et al.* (2006)	2004	5%	**20.238 €**

Year 2	£783	**915 €**	Karnon *et al.* (2006)	2004	5%	**1.227 €**
Year 3	£2242	**2.621 €**	Karnon *et al.* (2006)	2004	5%	**3.513 €**
Year 4	£589	**699 €**	Karnon *et al.* (2006)	2004	5%	**937 €**
Year 5	£592	**692 €**	Karnon *et al.* (2006)	2004	5%	**928 €**
Distant recurrence (5 years of Stage III BC)					Total	**48.734€**
Year 1	£10805	**12.633 €**	Karnon *et al.* (2006)	2004	5%	**16.930 €**
Year 2	£8380	**9.798 €**	Karnon *et al.* (2006)	2004	5%	**13.130 €**
Year 3	£4805	**5.618 €**	Karnon *et al.* (2006)	2004	5%	**7.529 €**
Year 4	£4804	**5.617 €**	Karnon *et al.* (2006)	2004	5%	**7.527 €**
Year 5	£2309	**2.700 €**	Karnon *et al.* (2006)	2004	5%	**3.618 €**
Terminal Phase (3month Stage IV BC)	£4941	**5.777 €**	Karnon *et al.* (2006)	2004	5%	**7.742 €**
Death from Breast Cancer	£3404	**3.980 €**	Mansel *et al.*(2007)	2003	5%	**5.600 €**
Death from other causes	£450	**526 €**	Mansel *et al.*(2007)	2003	5%	**740 €**
Ambulatory day care visit for drug infusion per drug cycle						
Drug Administration <1h[a]	Can$23	**17 €**	Dranitsaris *et al.* (2009)	2006	5%	**21 €**
Drug Administration 1-3h[b]	Can$45	**33 €**	Dranitsaris *et al.* (2009)	2006	5%	**41 €**
Drug Administration >3h[c]	Can$124	**92 €**	Dranitsaris *et al.* (2009)	2006	5%	**112 €**
HER-2 Test	€ 124	**124 €**	Macedo *et al.* (2009)	2009	5%	**130 €**

** 11/02/2011 exchange rate: 1 US$= 0,7266€; 1$Can=0,7415€; 1£ =1,1692€*

Table n. 36: Summary of BC costs literature review used in our model.

Source: Own construct.

Regard that, as most of the central hospital pharmacies treating breast cancer patients provide the exact amount of drug required and as any leftovers are saved for later use, no waste occurs. Therefore, the cost of medicines could be based on a simple multiplication of absolute dose in mg and drug price in EUR/mg. The drug price per mg was calculated as a weighted average of vial size-specific prices per mg, based on the vials needed for a woman with a body weight of 65 kg and a height of 1,62 m, assuming a typical Portuguese patient with a body-surface of $1.70m^2$, as considered in the study of Dranitsaris *et al.*, (2009).

2.3.2.2.5.3.3.4. CUA DATA: COUNTRY-SPECIFIC DISCOUNT RATE

For the alternatives to be comparable, the costs and consequences should occur at the same time period. This means that they need to be updated if they occur at different times, depending on the drug therapy protocol (different drugs may be administrated in different periods of time).
Incremental utilities, as well as costs, like transition probabilities, may though vary with time. One important application of this time dependence is the discounting used in CUA and CEA. This is based on the fact that costs or benefits occurring immediately are valued more highly than those occurring in the future. The discounting formula is:

$$U_t = \frac{U_0}{(1+d)^t}$$

where Ut, is the increment utility at time t, U0, is the initial incremental utility, and **d is the discount rate** (Sonnenberg & Beck, 1993).

Since the discount rate to be used solely reflects the pure time preference, there is no way to calculate it empirically. However, one can point an approximate value based on the real interest rate of the long-term capital market so, in Portugal, this discount rate takes the reference value of 5% for costs and consequences, similarly to the rate undertaken by most countries where there are methodological guidelines for carrying out economic evaluation studies. However, recent studies, such as the Washington Panel, pointed to a rate of 3%, so this value can also be used in a sensitivity analysis of a Portuguese study (Silva *et al.*,1998).

It is debatable whether or not valued consequences should be updated. In fact, if, for example, to appreciate the impact of alternatives by the number of life years gained, the updating means considering that the current value of one life year gained decreases with time (Dedes *et al*., 2009). However, failure to update the consequences induces biases, since it favors the alternative whose impact is felt in the long-term in detriment of those whose results occur in the shorter-term (Silva *et al*., 1998).

The role of discount rates was also considered an important factor by Annemans (2008). Indeed, discount rates present a key factor in the setting where costs and benefits accumulate over a long period of time with some major costs (notably adjuvant drug costs) occurring early and some major benefits (notably survival) occurring later.

Following the data presented, **in this work, future costs and consequences (QALYs) were discounted using a 5% discount rate per year.**

2.3.2.3. OUTPUT DATA

In the first assessments carried out, it was common practice to present the results through global costs and consequences of each alternative, but this form of presentation of the results was inappropriate for two reasons. First, since the comparison is always between treatments in the current practice, the decision is about which incur additional costs and additional benefits if the alternative replaces the usual procedure. Moreover, the comparison of overall results has implied that the costs and consequences associated with each alternative will behave as a uniform scale, increasing or decreasing over time at a steady rate. However, this may not happen. Consequently, the costs and consequences of each alternative should always be presented in terms of total increase (or decrease) compared with the standard therapy / practice. Otherwise, it runs the risk of obscuring the overall impact of the alternatives under consideration. Further, the presentation of total costs and consequences per therapy allows future users to compare the results with new drugs not included in the study or with results from other geographical contexts (regions or countries) (Silva *et al.*, 1998).
Though, as **output data**, will be estimated the impact of a pharmacological intervention on costs (annual costs per patient), consequences/utilities (quality adjusted life years per patient - QALYs) and on ICER.

The BC model is fully adaptable to allow the calculation of costs through an **hospital, clinical and third party healthcare payer (**NHS) **perspectives** for any given simulation (as the CORE diabetes model of Palmer *et al*, 2004[a]), since it is designed to be customized in order to meet audience specific-needs (a provider specific version of

the model) or purposes, as indicated in the next table, found in the *Portuguese Economical Evaluation os Medicines Guidelines.*

Purpose of the study	**Results to present**	**Where disseminate results**
Justify repayment or **reimbursement** of the price of the drug **by public entities**	**a. Total costs and consequences of each incremental alternative.** **b. Cost-Effectiveness Ratios, Cost-Effective or Cost-Utility of incremental global alternatives**, depending on the analysis technique chosen. c. Total incremental costs and consequences reflecting the perspective of public third payer. d. Cost-Effectiveness Ratios, Cost-Effective or Cost-Utility of incremental alternatives from the perspective of the third public payer, depending on the analysis technique chosen. e. Estimated impact of the adoption of the alternative proposed in the budget of the NHS drugs.	Documents for information on pricing and reimbursement
Doctors, pharmacists and medical opinion leaders	a. **Total costs and consequences of each incremental alternative.** b. **Cost-Effectiveness Ratios, Cost-Effective or Cost-Utility of incremental global alternatives,** depending on the analysis technique chosen. c. **Incremental costs and consequences reflecting the perspective of the health care provider.** d. Cost-Effectiveness Ratios, Cost-Effective or Cost-Utility of incremental alternatives from the perspective of the provider of care, depending on the analysis technique chosen.	Symposiums, conferences, scientific journals.

Table n. 37: Economic analysis study presentation, according to study purpose.
Source: Silva *et al.*, (1998).

2.3.2.3.1. COST-UTILITY ANALYSIS

Total costs and QALYs were calculated as functions of the stages of BC complications reached during five and ten years of simulation, plus any acute events that may occur during that period. Acute event costs are accounted as they occur but stage costs and utilities are accounted semiannually and are cumulative (Palmer *et al*, 2004[a]).
The results of the recent economic evaluation analyses consistently showed that outputs of this kind of studies are expressed in terms of **Costs (€, £ or US$)** per **quality adjusted life-year (QALY) gained** (Dranitsaris *et al*., 2009; Karnon *et al*., 2006; Karnon & Brown, 2002; Kurian, *et al.*, 2007; Liberato, Marchetti & Barosi, 2007), which supports the common use of CUA analysis technique, like previously referred.

Next, we present the result of the output variables described through the three perspectives contemplated in our model.

Oncologist Perspective

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,02111	0,04469	0,02358	0,97	115,00 €	74,13 €	99%	99	0,04	0,03	
I	4,60443	11,12814	6,52371	0,84	161.939,98 €	104.386,51 €	92%	72	7,96	5,13	
II	11,43739	26,40431	14,96692	0,64	376.449,00 €	242.659,03 €	74%	58	15,19	9,79	**Cost per QALY per person**
III	4,52457	10,09017	5,56561	0,61	321.182,11 €	207.033,99 €	56%	44	4,39	2,83	
IV	2,13175	4,72593	2,59418	0,26	36.588,18 €	23.584,74 €	14%	11	0,51	0,33	
				Total	**896.274,28 €**	**577.738,40 €**			**28,10**	**18,12**	**31.891,79 €**

Table n. 38: CHEAUL BC model outputs, from the oncologist perspective.

Source: Own Construct.

Hospital Perspective

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,01056	0,02235	0,01179	0,97	115,00 €	74,13 €	99%	99	0,02	0,01	
I	2,29883	5,44613	3,14730	0,84	80.430,61 €	51.845,57 €	92%	72	3,90	2,51	
II	5,73433	13,41442	7,68009	0,64	189.556,47 €	122.188,10 €	74%	58	7,72	4,98	**Cost per QALY per person**
III	2,29551	5,09409	2,79858	0,61	162.495,89 €	104.744,85 €	56%	44	2,22	1,43	
IV	1,04441	2,34517	1,30077	0,26	18.156,34 €	11.703,58 €	14%	11	0,26	0,16	
				Total	**450.754,31 €**	**290.556,23 €**			**14,11**	**9,09**	**31.948,07 €**

Table n. 39: CHEAUL BC model outputs, from the hospital perspective.

Source: Own Construct.

NHS Perspective

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,00193	0,00432	0,00240	0,97	115,00 €	74,13 €	99%	99	0,00	0,00	
I	0,38630	0,87391	0,48760	0,84	13.357,76 €	8.610,41 €	92%	72	0,63	0,40	
II	0,95850	2,16905	1,21055	0,64	31.344,96 €	20.204,96 €	74%	58	1,25	0,80	**Cost per QALY per person**
III	0,38154	0,83420	0,45267	0,61	26.782,54 €	17.264,02 €	56%	44	0,36	0,23	
IV	0,17582	0,38626	0,21044	0,26	2.990,46 €	1.927,65 €	14%	11	0,04	0,03	
				Total	**74.590,72 €**	**48.081,18 €**			**2,28**	**1,47**	**32.677,85 €**

Table n. 40: CHEAUL BC model outputs, from the NHS perspective.

Source: Own Construct.

Analyzing the tables presented above, we can see that there is an error associated with the model, because the proportion os Costs and QALYs should have been the same for the BC therapy most commonly used. The results major variation was from 31.891,79€/QALY per person (oncologist perspective) to 32.677,85€/QALY per person (NHS perspective), indicating a dispersion of 2,46%. However, if we recall that **NHS perspective** is targeted to State decision-makers and though, matrix probabilities were assigned specifically regarding the **number of women in the country** (the only data that has to be collected by this professionals regarding the CHEUAL matrix), that in our days is around 55.000 people; that the **hospital perspective** is prepared for *Hospital´s Pharmacy and Therapeutics Commission* to simply consider the total **number of BC incidence in the country and hospital cancer treatment rate;** and that the **oncologist perspective** matrix probabilities accounted specifically with the **number of BC patients that the physician is expecting to assist each year of one specific type of tumor (HER-2 +/ER- or HER-2-/ER+**, that are adequate for completely different types of therapy protocols), we are assuming a huge probability difference from millions, to thousands, to hundreds or even tens, respectively. This indicates that the 2,46% error presented isn´t significant, considering the reality difference in comparison.

Other fact to point is that in our model we also considered the **ICER**, expressed as cost per quality adjusted life-year QALY, the main model output. However, this wasn´t yet calculated because its purpose is to provide an assessment of the extra costs and benefits of an intervention when compared with another treatment option (Brown, Lipscomb & Snyder, 2001), and this we will only regard in the model application chapter (discussed later). However, as we are contemplating output measures, its timely to appreciate this ratio impact.

In fact, according to Lamers, Groot & Buijt (2007) and to Banta & Wit (2008), ICER, is playing a significant role in some difficult, and very high profile, technology appraisal decisions.

Some economists, however, would complain that it is a bastardised form of cost-effectiveness that has long ceased to be a true indicator of how society should act to maximize economic welfare. Certainly NICE has quite explicitly and unashamedly set out its decision framework – one in which economic evaluation uses a multinomial

approach to try to better identify how to maximize health gain within a pre-determined and limited budget for health services. It largely ignores costs outside the NHS and personal social services and benefits that do not constitute health improvements. But it does take a long-term perspective, it does ignore budgetary boundaries within health and it does attempt to be evidence based (Buxton, 2006).

In CUA, ICER can be calculated by the following formula:

$$\mathbf{ICER = (C_A\text{-}C_B)/(U_A\text{-}U_B),}$$

being C_A, the global cost of therapy option A; C_B, the global cost of therapy option B; U_A, the therapy option A utility (in QALYs) and U_B, the therapy option A utility (in QALYs also) (Banta & Wit, 2008).

In published economic evaluation studies, the ICER must be compared to a willingness to pay threshold.

2.3.2.3.2. WILLINGNESS-TO-PAY THRESHOLD

The threshold represents the opportunity cost of the implementation of a certain (new) therapy option (the health gain forgone by other patients). While the threshold is critical to the determination of the most efficient (health maximizing) use of NHS resources, the Appraisal Committee also considers whether there is any ground in equity for weighting the health gains and losses of different people or for recommending technologies with relatively high ICERs (McCabe, Claxton & Culyer, 2008).
An important further consideration relates to the wider opportunity cost of Appraisal Committee decisions. When the threshold is being used to allocate a fixed budget, there is not one category of patients interest, but two: those patients who would receive the new treatment or some alternative, and those patients who bear the opportunity cost of its provision (those whose service availability is reduced by virtue of the expenditure on the new treatment).

Ideally, the ICER threshold value is chosen so that it results in the most efficient use of a predetermined health budget. In this case, the threshold has to be set to ensure that, at the margin, adopted technologies have a better cost per QALY ratio, than the ratio of any technologies that are not adopted or that have to be disinvested in order to free resources (Buxton, 2006).

The resulting ICERs must therefore be compared with a **willingness-to-pay threshold**. Remind that the nature of the threshold value for the ICER – the maximum value that it is prepared to pay for a QALY – has emerged only slowly. For a considerable period, the existence of this threshold value was denied. However, in 2004, NICE published a revised methodological guidance on technology appraisal and thresholds became more transparent (Buxton, 2006).

When the implications of cost-utility results for reimbursement decisions are discussed, reference to **thresholds** (derived from comparison of different interventions or based on society willingness-to-pay) is usually made, representing the health expected to be forgone elsewhere in the National Health Service because of the additional costs (Claxton, 2008).
In analyses for the USA, threshold values of USD 50.000–100.000 per QALY gained are usually regarded as acceptable (Dedes *et al*., 2009). This means that, a QALY is expected to be lost for every USD 50.000-100.000 the NHS must find by curtailing other activities to accommodate the use of a more costly technology (Claxton, 2008). More recently, "anecdotal comments from the UK-based National Institute for Clinical Excellence indicate that between £20 000 and £30 000 is an acceptable range for cost per QALY within the UK context" (Brown, Lipscomb & Snyder, 2001). The precise wording is as it follows (Buxton, 2006):
"*Below a most plausible ICER of £20 000/QALY, judgments about the acceptability of a technology as an effective use of NHS resources are based primarily on the cost-effectiveness estimate. Above a most plausible ICER of £20 000/QALY, judgments about the acceptability of the technology as an effective use of NHS resources are more likely to make more explicit reference to factors including:*

- *the degree of uncertainty surrounding the calculation of ICERs*
- *the innovative nature of the technology*

- *the particular features of the condition and population receiving the technology*
- *where appropriate, the wider societal costs and benefits.*

Above an ICER of £30 000/QALY, the case for supporting the technology on these factors has to be increasingly strong. The reasoning for the Committee's decision will be explained, with reference to the factors that have been taken into account, in the Considerations' section of the guidance."

According to Buxton (2006), basically there are two broad approaches for determining an appropriate threshold value for a QALY. The first approach is based on some concept of social valuation: the value that the public, or politicians on their behalf, places on an additional QALY. This would require some process of elicitation using willingness-to.pay or associated techniques. The result would be that the derived value would then effectively determine how much should be spent on health. Though, CEA and CUA should be used to identify any opportunities that exist to generate incremental QALYs for less than the threshold defined. In principle, then, the cost of the resultant set of cost-effective technologies would define the healthcare budget. The alternative conceptual approach is that the ICER threshold value is chosen so that it results in the most efficient use of a predetermined health budget. In this case, the threshold has to ensure that, at the margin, adopted technologies have a better cost-effectiveness ratio than the cost- effectiveness ratios of any technologies that are not adopted or that have to be disinvested in order to free resources.

However, other countries haven't formally defined such thresholds yet, and Portugal is one of them. If differences in purchasing power parity are taken into account, this range is roughly equivalent to €31,000–62,000 per QALY gained (Dedes *et al*., 2009). This threshold corresponds to 0,25-0,50 times the Portuguese gross domestic product (GDP) per capita (INE, 2009).

So, in the present case, the resulting ICERs will be compared with a **willingness-to-pay threshold of 50,000 €/QALY.** This same threshold was previously used/calculated in the studies of, Dedes *et al*. (2009), McKeage & Lyseng-Williamson (2008), Quagari *et al.* (2007), Skedgel, Rayson & Younis (2009), Thompson *et al.* (2007), Neyt, Albrecht & Cocquyt (2006), and Liberato, Marchetti & Barori (2007).

However, healthcare purchasers are concerned not just with maximizing efficiency but also with affordability and the goal of remaining within annual budgets, which can be achieved through **budget impact analysis.** Based on the open cohort simulation, users can specify the percentage of patients receiving various treatments in addition to prevalent and incidence cohort characteristics, and perform budget impact analysis over short or long-term time horizon. This analysis, although not considered in this study, is assumed of extreme importance, and eventually, a target for future investigations.

3.EMPIRICAL STUDY

3.1. MODEL VALIDATION

Simulation models need to be validated before they can be believed and used for decision making. From the perspective of the health care simulations, the validation process asks whether or not the model is internally consistent and if is consistent with the real world clinical system being study (Stahl, 2008). Simulation model internal validation typically proceeds by systematically exploring the behavior of the model through sensitivity analysis, as we shall see bellow.

According to this author, **sensitivity analysis** is the procedure in which the assumptions underlying the model are challenged and the variables representing those assumptions are systematically varied. This process allows one to determine to what variables the decision strategy or system modeled is sensitive. A decision may be considered sensitive to a variable if changing it within a plausibly defined range, results in a change in which strategy is favored (for example, changing from surgical to medical therapy). This allows users to estimate uncertainty in results from the model and to evaluate the influence of key variables in any given situation (Dedes *et al*., 2009, Palmer *et al*, 2004[a]).

Regarding the *Portuguese Drugs Economic Evaluation Guidelines* (Silva *et al*., 1998), in most studies, the results reflect little robust estimates of the variables. If the values are obtained from population samples or clinical trials, sensitivity analysis should be based on confidence intervals for which results were obtained.
Alternatively, when there are doubts about the accuracy of the data used (for example, with the amounting of some categories of costs, or on which hospital costs to consider, using a weighted average of various types of hospitals or using data only relating to the central hospitals), the sensitivity analysis should be done considering the ranges of parameter values in question ("threshold analysis") or by providing estimates for these values.

Our study was based on data from the Portuguese population, alongside this data from the main central Portuguese oncologic hospital, as well as with data from international literature and clinical trials, reason why we chose to opt by the second technique.
In this technique, the analysis is done by specifying alternative values for parameters and comparing the results reached with the initial scenario. As no confidence intervals were available for most of these parameters, their base case values were varied by ±25% (as in the study of Lundkvist *et al.*, 2007, for example).
If there are controversy standards of assessment, all alternatives should be considered (Silva *et al*., 1998). Therefore, we tested the variance of twenty variables (previously identified as the hypotheses to test), the ones that integrate the model construct and considered to have a significant positive influence in the model outcome.

In summary, there are two common types of sensitivity analyses in use in economic evaluations studies, and each addresses different types of uncertainty: one way and probabilistic sensitivity analysis (Stahl, 2008).

One-way sensitivity analysis (Dranitsaris *et al*., 2009) will be performed to test the robustness of the cost-utility outcomes measured. When one parameter is varied in this way, it is referred to as *one-way sensitivity analysis*. This technique was used in the economic studies of Dranitsaris *et al.* (2009); Dedes *et al.* (2009); Neyt, Albrecht & Cocquyt (2006); Lindgren, Jonsson, Redaelli & Radice (2002); Lundkvist *et al.* (2007); Norum, Olsen, Wist & Lonning (2007); Nuijten Cormick, Waibel & Parison (2007); Dedes, Szucs, Imesch, Fedier, Fehr & Fink, (2007); Garrison, Lubeck, Lalla, Paton, Dueck & Perez (2007); Onukwugha, Mullins & DeLisle (2008); Neyt, Huybrechts, Hulstaert, Vrijens & Ramaeckers (2007); and Lyman, Lalla, Barron & Dubois, (2009).

Probabilistic sensitivity analysis (second-order Monte Carlo Simulation) (Karnon *et al.*, 2006; Kurian, A *et al.*, 2007; Liberato *et al.*, 2007) to access the impact of statistical uncertainty around key model inputs (Dedes *et al*., 2009) is also of great importance, but unfortunately it could not be tested because we weren´t able to access the adequate software at the time of this study.
Probabilistic sensitivity analysis usually refers to simultaneous consideration of all the uncertainties surrounding the variables in the model, usually as stochastic distributions

in a Monte Carlo Simulation model. However, it is less useful for determining specific variables that the strategy is sensitive to. Note that, just as in *n*-way sensitivity analysis, caution must be taken to ensure that the model inputs being examined are not correlated and giving a false impression of causality. Therefore, according to Stahl (2008), before running multi-dimensional sensitivity analysis, it is a good technique to examine your model inputs using standard statistical techniques for correlation or, if the data allows, use causal analysis to identify the key variable driving correlated behavior. This was our priority.

However, in the study of Andronis, Barton & Bryan (2009), strong support was expressed for probabilistic sensitivity analysis, mainly because it provides an indication of the parameter uncertainty around the ICER.

Second order Monte Carlo Simulation analysis were found in the studies of Weinstein (2006), Dedes *et al.* (2009), Metropolis & Ulam (1949), Liberato, Marchetti & Barori (2007), Kurian *et al.* (2007), Mansel *et al.* (2007), Martin *et al.* (2003), Quagari *et al*. (2007), Shiroiwa *et al.* (2008), Thompson *et al.* (2007), KelloKumpu-Lehtinen, Bergh, Salminen, Wiklund, Lehtinen, Aronen & Sintonen, (2007), Neyt *et al*. (2007), Lyman *et al.* (2009), Lidgren *et al.* (2008), and Onukwugha, Mullins & DeLisle (2008).

We can then address the question of under what conditions the model is stable and under what conditions is it not, providing us with a sense of the strength of the evidence generated by the model. Note that **the global current therapy cost per QALY ratio found in every perspective, was below the willingness-to-pay threshold assigned**, of 50.000€/QALY.

One of the aims of this study, based on the work of Palmer *et al* (2004[b]) was also to access external validity of the CHEUAL breast cancer model, or to test the ability to predict intermediate and long-term outcomes by comparing the results (correlating the data) from CHEAUL model simulations/predictions with observed outcomes from published epidemiological and clinical studies in breast cancer, used and not used to construct the model. However, this turned not to be possible, since we hadn´t any BC study which used the same BC cytostatic treatment protocol used in IPOL (and that was considered to represent country reality).

3.2. METHODOLOGY

In this study, the research strategy adopted was mainly quantitative, congregating biographical, clinical and experiment research.

The technique for data collection used was the collection of documents and of clinical data.

To the first, scientific papers and legal organizational documents were collected with the help of the B-On database, that incorporates the following databases: Annual reviews, Elsevier – science direct, Springer Link (Springer/kluwer), Wiley Interscience (Wiley), Academic search complete (EBSCO), Pub Med, Web of Science (ISI), Current Contents (ISI), ISI Proceedings (ISI) and RCAAP; the key-words used to find the desired documents were: "cost-effectiveness + breast cancer", "cost-utility + breast cancer", "cost-utility + decision-making", "cost-effectiveness + decision-making" or "breast cancer economic evaluation + Markov model + Monte Carlo simulation model", "Breast Cancer + Acute renal failure", "Breast Cancer + Acute Hepatic Failure", "Breast Cancer + Cardiovascular Disease", "Breast Cancer + Acute Arthralgia", "Breast Cancer + Acute Diarrhea", "Breast Cancer + Acute Cytopenia", "Breast Cancer + Osteoporosis"; "Breast Cancer + Acute Pulmonary Disease")

The literature review also included a search in available relevant databases such as: Administration Central Health System (ACSS), INFARMED (National Authority of Medicines and Health Products), Organization World Health, Statistics Portugal, INE (Statistic National Institute), National Observatory Health Systems (ONSA), Directorate General of Health, Organization for Economic Cooperation and Development (OECD), Globocan 2002, Medline, IMS Lifecycle, IMS MIDAS, and IMS Knowledge Link.

Priority was given to Portuguese official documents. When Portuguese official data was not available, we resorted to international data from WHO and OECD. The data used was always the most recently published, or the one that explored models or economic evaluation techniques in detail (usually the first to be published on the matter), for better understanding.

Clinical data was collected in the IPOL (Portuguese Institute of Oncology of Lisbon), the fifth Portuguese hospital more expensive in terms of drug consumptions, representing 6,1% of hospitals´ drug consumption of the country (INFARMED, 2009), and though considered representative of national clinical practice.

Note that during the development of the CHEUAL BC model, an extensive literature research was performed to identify appropriate data sources for the model. Studies were selected based on previously defined criteria, like the presentation of appropriate data provided, and the availability of recent and largest randomized clinical trials. Preference was then given to epidemiological studies which collected "real life" data over a long period of follow-up rather than comparative controlled clinical trials. However, this is difficult to avoid given the majority of data used to create any disease model, that must come from clinical studies of that disease.

As recommended by the *Portuguese economic evaluation of drugs methodological guidelines* (Silva *et al.*, 1998), as sources of data, were privileged the results from a causal relationship (effectiveness or efficacy of a therapeutic intervention), obtained from randomized controlled trials, methodologically valid and relevant to the country; or from a meta-analysis of clinical trials, with these characteristics.

Within these, we had privileged the data obtained retrospectively on the effectiveness in terms of current clinical practice, although it is also permissible to use efficacy data from appropriate clinical trials, corrected by modeling. It is also accepted the use of effectiveness data obtained from observational epidemiological studies. In any case, the national reality and in particular the technologies / medical strategies most used were reflected. Statistical data regarding the epidemiology of the disease or related complications was obtained, whenever possible, from population-based epidemiological studies. In any case, the source of data used and the assumptions were clearly specified. We also presented socio-demographic characteristics of the population, description of pathology and current clinical practice.

The scientific quality criteria implicit in this research included the CHEUAL BC model construct and validity, through one way sensitivity analysis.

3.3. RESULTS AND DISCUSSION

We will start presenting the summary of the validation process, in the following chart, and then we will analyze each variable variation independently.

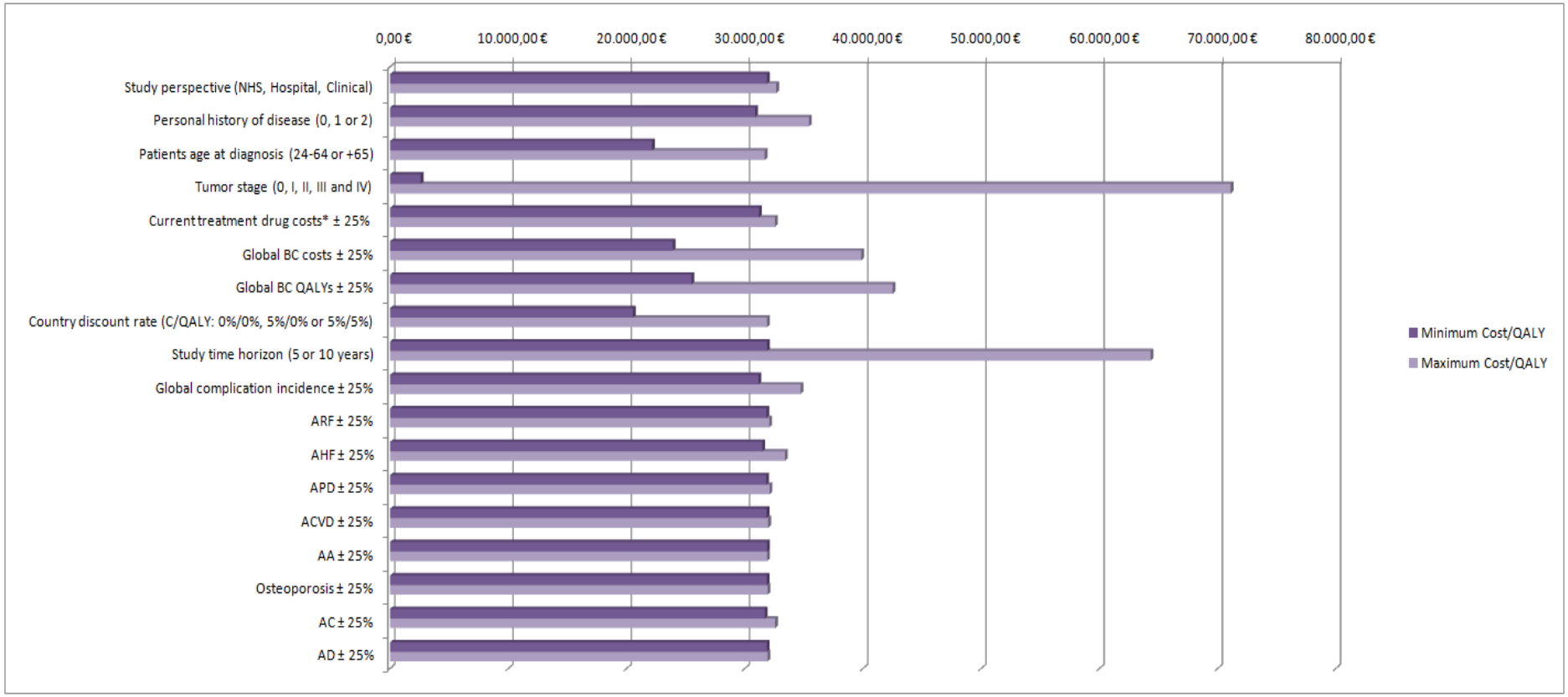

Chart n.9: BC CHEUAL model one way sensitivity analysis results. Source: Own calculations.

In the next table it is possible to better visualize the Cost per QUALY per person variation. When there wasn´t a specific internal variable variation hypothesis to be tested (following the main variable variation adopted by other authors, as Mansel *et al.* (2007), for example), we decided to vary the variables in 25% (as in the study of Lundkvist *et al.*, 2007) and check the impact on C/QALY ratio. The threshold chosen to validate a positive impact or influence on the model outputs, was a variation ≥ 2,5% (of 10% of the variation induced).

	Variation (%)
Study perspective (NHS, Hospital, Clinical)	2,46
Personal history of disease (0, 1 or 2)	14,67
Patients age at diagnosis (24-64 or +65)	42,94
Tumor stage (0, I, II, III and IV)	2636,42
Current treatment drug costs* ± 25%	4,34
Global BC costs ± 25%	66,67
Global BC QALYs ± 25%	66,67
Country discount rate (C/QALY: 0%/0%, 5%/0% or 5%/5%)	55,13
Study time horizon (5 or 10 years)	101,80
Global complication incidence ± 25%	11,44
ARF ± 25%	0,74
AHF ± 25%	6,06
APD ± 25%	0,87
ACVD ± 25%	0,45
AA ± 25%	0,01
Osteoporosis ± 25%	0,22
AC ± 25%	2,75
AD ± 25%	0,18
*ambulatory day care visit, drug, and drug preparation and administration costs	

Table n.41: BC CHEUAL model one way sensitivity analysis variation results summary.

Source: Own calculations.

The first C/QALY ratio variation relates to the differences regarding the application of the model through the different considered perspectives. As discussed before, this variation is not significant, which means that the **first hypothesis (H1) previously proposed**, of the study perspective having a positive influence in the model output, **have to be rejected**, in agreement to what we were supposing. On the other hand, this fact lead us to the ability of validating all the variables to be tested in just one of the perspectives and assuming the same result to the others (namely, through the clinical perspective).

(New) Therapy option drug costs output variation can only be analyzed after the model application presentation (discussed later).

The personal history of disease related to probable therapy toxicity, however, presented a variation of 14,5%. Following the reasoning just presented, the **third hypothesis (H3) was accepted**, proving that the personal history of disease positively influence the model output, as expected. The correspondent calculations are presented in the tables below.

No previous history of complications

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,01056	0,02273	0,01217	0,97	115,00 €	74,13 €	99%	99	0,02	0,01	
I	2,39678	5,79540	3,39862	0,84	84.306,55 €	54.344,00 €	92%	72	4,15	2,67	
II	5,95640	13,65624	7,69984	0,64	195.608,92 €	126.089,51 €	74%	58	7,86	5,06	**Cost per QALY per person**
III	2,00804	4,54589	2,53785	0,61	143.769,58 €	92.673,87 €	56%	44	1,98	1,28	
IV	0,90035	2,04981	1,14946	0,26	15.869,64 €	10.229,57 €	14%	11	0,22	0,14	
				Total	439.669,70 €	283.411,09 €			14,23	9,17	**30.902,86 €**

Table n. 42: CHEAUL BC model output calculations after variable variation: No previous history of complications.

Source: Own calculations.

Previous history of complication

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,00577	0,01205	0,00628	0,97	115,00 €	74,13 €	99%	99	0,01	0,01	
I	1,32919	3,24770	1,91851	0,84	46.883,19 €	30.220,90 €	92%	72	2,32	1,50	
II	3,31044	7,62587	4,31543	0,64	108.882,34 €	70.185,56 €	74%	58	4,39	2,83	**Cost per QALY per person**
III	1,17216	2,62118	1,44901	0,61	83.336,75 €	53.718,87 €	56%	44	1,14	0,74	
IV	0,52103	1,17305	0,65202	0,26	9.081,76 €	5.854,10 €	14%	11	0,13	0,08	
				Total	**248.299,03 €**	**160.053,56 €**			**7,99**	**5,15**	**31.070,42 €**

Table n. 43: CHEAUL BC model output calculations after variable variation: Previous history of one complication.

Source: Own Calculations.

Previous history of two complications

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,00478	0,00991	0,00513	0,97	115,00 €	74,13 €	99%	99	0,01	0,01	
I	0,87846	2,08504	1,20658	0,84	30.750,24 €	19.821,61 €	92%	72	1,49	0,96	
II	2,17056	5,12220	2,95164	0,64	71.957,74 €	46.383,96 €	74%	58	2,95	1,90	**Cost per QALY per person**
III	1,34437	2,92311	1,57874	0,61	94.075,78 €	60.641,25 €	56%	44	1,27	0,82	
IV	0,71037	1,50307	0,79270	0,26	11.636,79 €	7.501,07 €	14%	11	0,16	0,11	
				Total	**208.535,55 €**	**134.422,01 €**			**5,88**	**3,79**	**35.437,31 €**

Table n. 44: CHEAUL BC model output calculations after variable variation: Previous history of two complications.

Source: Own calculations.

The patients age at diagnosis/age grouping presented a variation of 42,94%. Following the reasoning presented, the **fourth hypothesis (H4) was accepted**, proving that the personal history of disease much positively influence the model output, as expected. The correspondent calculations are presented in the tables below.

24-64years

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,01055	0,02234	0,01179	0,97	115,00 €	74,13 €	99%	99	0,02	0,01	
I	0,00528	5,41761	5,41233	0,84	20.886,33 €	13.463,33 €	92%	72	3,88	2,50	
II	1,19810	13,22934	12,03124	0,64	87.984,44 €	56.714,77 €	74%	58	7,61	4,91	**Cost per QALY per person**
III	2,97095	5,05289	2,08194	0,61	182.448,55 €	117.606,33 €	56%	44	2,20	1,42	
IV	1,00207	2,36491	1,36283	0,26	18.309,10 €	11.802,05 €	14%	11	0,26	0,17	
				Total	**309.743,42 €**	**199.660,61 €**			**13,97**	**9,00**	**22.177,93 €**

Table n. 45: CHEAUL BC model output calculations after variable variation: 24-64years. Source: Own calculations.

≥65years

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,01056	0,02235	0,01179	0,97	115,00 €	74,13 €	99%	99	0,02	0,01	
I	2,30193	5,71053	3,40860	0,84	81.523,49 €	52.550,04 €	92%	72	4,08	2,63	
II	5,70795	13,17496	7,46701	0,64	187.859,77 €	121.094,41 €	74%	58	7,58	4,89	**Cost per QALY per person**
III	2,26008	5,03728	2,77720	0,61	160.382,41 €	103.382,50 €	56%	44	2,19	1,41	
IV	1,06649	2,36103	1,29454	0,26	18.279,08 €	11.782,69 €	14%	11	0,26	0,17	
				Total	**448.159,74 €**	**288.883,77 €**			**14,14**	**9,11**	**31.700,49 €**

Table n. 46: CHEAUL BC model output calculations after variable variation: ≥ 65 years. Source: Own calculations.

Tumor stage presented a variation the biggest variation, of 2636,42%. Following the reasoning presented, the **fifth hypothesis (H5) was accepted**, proving that the BC stage had the strongest positively influence of the model output, as expected. The correspondent calculations are presented in the table below.

Ratio C/QALY per BC Stage

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	**Cost/QALY per Stage**
0	0,02111	0,04469	0,02358	0,97	115,00 €	74,13 €	99%	99	0,04	0,03	**2.599,21 €**
I	4,60443	11,12814	6,52371	0,84	161.939,98 €	104.386,51 €	92%	72	7,96	5,13	**20.344,32 €**
II	11,43739	26,40431	14,96692	0,64	376.449,00 €	242.659,03 €	74%	58	15,19	9,79	**24.779,88 €**
III	4,52457	10,09017	5,56561	0,61	321.182,11 €	207.033,99 €	56%	44	4,39	2,83	**73.107,89 €**
IV	2,13175	4,72593	2,59418	0,26	36.588,18 €	23.584,74 €	14%	11	0,51	0,33	**71.125,40 €**
				Total	896.274,28 €	577.738,40 €			28,10	18,12	**31.891,79 €**

Table n. 47: CHEAUL BC model output calculations after variable variation: Ratio C/QALY per BC Stage.

Source: Own calculations.

Current treatment drug costs presented a variation of 4,34%. Following the reasoning presented, the **sixth hypothesis (H6) was accepted**, proving that the current drug costs positively influence the model output, as expected. The correspondent calculations are presented in the tables below. Note that drug costs encompass ambulatory day hospital visit costs, drug costs and preparation and administration costs (according to the time needed to complete the cytostatic therapy administration per chemo-endocrine-immunotherapy cycle).

Current drug costs +25%

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,02111	0,04469	0,02358	0,97			99%	99	0,04	0,03	
I	4,60443	11,12814	6,52371	0,84			92%	72	7,96	5,13	
II	11,43739	26,40431	14,96692	0,64			74%	58	15,19	9,79	**Cost per QALY per person**
III	4,52457	10,09017	5,56561	0,61			56%	44	4,39	2,83	
IV	2,13175	4,72593	2,59418	0,26			14%	11	0,51	0,33	
				Total	**915.296,71 €**	590.000,26 €			**28,10**	**18,12**	**32.568,66 €**

Table n. 48: CHEAUL BC model output calculations after variable variation: additional 25% current drug costs. Source: Own calculations.

Current drug costs -25%

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,02111	0,04469	0,02358	0,97			99%	99	0,04	0,03	
I	4,60443	11,12814	6,52371	0,84			92%	72	7,96	5,13	
II	11,43739	26,40431	14,96692	0,64			74%	58	15,19	9,79	**Cost per QALY per person**
III	4,52457	10,09017	5,56561	0,61			56%	44	4,39	2,83	
IV	2,13175	4,72593	2,59418	0,26			14%	11	0,51	0,33	
				Total	**877.251,85 €**	565.476,54 €			**28,10**	**18,12**	**31.214,92 €**

Table n. 49: CHEAUL BC model output calculations after variable variation: 25% decrease current drug costs. Source: Own calculations.

Therapy costs varying through drug costs 25% variation were calculated as follows:

	Drug Cost	Additional 25%	25% Decrease	
FEC	26.436,46 €	33.045,57 €	19.827,34 €	Therapy Cost:
Tamoxifen	99,56 €	124,45 €	74,67 €	896.274,28 €
Letrozole	1.141,00 €	1.426,25 €	855,75 €	No drug Therapy Cost:
TAC	6.081,04 €	7.601,30 €	4.560,78 €	820.184,55 €
Trastuzumab	26.637,57 €	33.296,97 €	19.978,18 €	Total therapy Cost -25%
5-Fluoruracilo	15.694,10 €	19.617,62 €	11.770,57 €	877.251,85 €
				Total Therapy Cost +25%
				915.296,71 €

Table n. 50: Current drug costs impact on therapy costs. Source: Own calculations.

The global BC therapy cost presented a variation of 66,67%. Following the reasoning presented, the **seventh hypothesis (H7) was accepted**, proving that this variable much positively influence the model output, as expected. The correspondent calculations are presented in the tables below.

Global therapy cost +25%

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,02111	0,04469	0,02358	0,97			99%	99	0,04	0,03	
I	4,60443	11,12814	6,52371	0,84			92%	72	7,96	5,13	
II	11,43739	26,40431	14,96692	0,64			74%	58	15,19	9,79	**Cost per QALY per person**
III	4,52457	10,09017	5,56561	0,61			56%	44	4,39	2,83	
IV	2,13175	4,72593	2,59418	0,26			14%	11	0,51	0,33	
				Total	**1.120.342,85€**	722.173,00 €			**28,10**	**18,12**	**39.864,74 €**

Table n. 51: CHEAUL BC model output calculations after variable variation: Additional 25% therapy cost.

Source: Own calculations.

Global therapy cost -25%

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,02111	0,04469	0,02358	0,97			99%	99	0,04	0,03	
I	4,60443	11,12814	6,52371	0,84			92%	72	7,96	5,13	
II	11,43739	26,40431	14,96692	0,64			74%	58	15,19	9,79	**Cost per QALY per person**
III	4,52457	10,09017	5,56561	0,61			56%	44	4,39	2,83	
IV	2,13175	4,72593	2,59418	0,26			14%	11	0,51	0,33	
				Total	**672.205,71 €**	433.303,80 €			**28,10**	**18,12**	**23.918,84 €**

Table n. 52: CHEAUL BC model output calculations after variable variation: 25% Decrease of therapy cost.

Source: Own calculations.

A number of studies that mainly focused on the direct costs of breast cancer at different stages have shown that these costs are highest following diagnosis and initial treatment due to surgery, hospitalization and possibly chemotherapy and/or radiation therapy. They decrease significantly during the continuing-care stage and increase again in the later stage of the disease before death, mainly for hospitalization (Radice & Redaelli, 2003). Our study reinforce this idea, by the results presented.

Based on these results, we can assume that interventions (e.g. screening) preventing cancer will afford the greatest immediate cost savings.

The global BC QALY cost presented a variation of 66,67%. Following the reasoning presented, the **eighth hypothesis (H8) was accepted**, proving that this variable much positively influence the model output, as expected. The correspondent calculations are presented in the tables below.

Global QALY cost +25%

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,02111	0,04469	0,02358	0,97	115,00 €	74,13 €	99%	99	0,02111	0,04469	
I	4,60443	11,12814	6,52371	0,84	161.939,98 €	104.386,51 €	92%	72	4,60443	11,12814	
II	11,43739	26,40431	14,96692	0,64	376.449,00 €	242.659,03 €	74%	58	11,43739	26,40431	**Cost per QALY per person**
III	4,52457	10,09017	5,56561	0,61	321.182,11 €	207.033,99 €	56%	44	4,52457	10,09017	
IV	2,13175	4,72593	2,59418	0,26	36.588,18 €	23.584,74 €	14%	11	2,13175	4,72593	
				Total	896.274,28 €	577.738,40 €			**35,13**	**22,64**	**25.513,43 €**

Table n. 53: CHEAUL BC model output calculations after variable variation: Additional 25% QALY cost. Source: Own calculations.

Global QALY cost -25%

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,02111	0,04469	0,02358	0,97	115,00 €	74,13 €	99%	99			
I	4,60443	11,12814	6,52371	0,84	161.939,98 €	104.386,51 €	92%	72			
II	11,43739	26,40431	14,96692	0,64	376.449,00 €	242.659,03 €	74%	58			**Cost per QALY per person**
III	4,52457	10,09017	5,56561	0,61	321.182,11 €	207.033,99 €	56%	44			
IV	2,13175	4,72593	2,59418	0,26	36.588,18 €	23.584,74 €	14%	11			
				Total	896.274,28 €	577.738,40 €			**21,08**	**13,59**	**42.522,39 €**

Table n. 54: CHEAUL BC model output calculations after variable variation: 25% Decrease of QALY cost. Source: Own calculations.

The country discount rate discounting both costs and consequences or just costs presented a variation of 55,13%. Following the reasoning presented, the **nineth hypothesis (H9) was accepted**, proving that this variable much positively influence the model output, as expected. The correspondent calculations are presented in the table below.

Country discount rate

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,02111	0,04469	0,02358	0,97	115,00 €	74,13 €	99%	99	0,04	0,03	**Cost per QALY per person 0/0%**
I	4,60443	11,12814	6,52371	0,84	161.939,98 €	104.386,51 €	92%	72	7,96	5,13	**31.891,79 €**
II	11,43739	26,40431	14,96692	0,64	376.449,00 €	242.659,03 €	74%	58	15,19	9,79	**Cost per QALY per person 5/0%**
III	4,52457	10,09017	5,56561	0,61	321.182,11 €	207.033,99 €	56%	44	4,39	2,83	**20.557,45 €**
IV	2,13175	4,72593	2,59418	0,26	36.588,18 €	23.584,74 €	14%	11	0,51	0,33	**Cost per QALY per person 5/0%**
				Total	896.274,28 €	577.738,40 €			28,10	18,12	**31.891,79 €**

Table n. 55: CHEAUL BC model output calculations after variable variation: Discount rate.

Source: Own calculations.

The time horizon of the study, between five and ten years, presented a variation of 101,80%. Following the reasoning presented, the **tenth hypothesis (H10) was accepted**, proving that this variable has a very strong positively influence in the model output; as expected the first years have additional expense (due to procedures as surgery, internment, RT, etc), with a consequent C/QALY ratio increase. The correspondent calculations are presented in the table below.

5 years time horizon

BC Stages	5 years Total Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,02111	0,97	57,58 €	37,12 €	99%	0,02	0,01	
I	4,60443	0,84	136.953,86 €	88.280,46 €	92%	3,56	2,29	
II	11,43739	0,64	307.003,51 €	197.894,46 €	74%	5,38	3,47	
III	4,52457	0,61	220.502,22 €	142.135,73 €	56%	1,55	1,00	**Cost per QALY**
IV	2,13175	0,26	16.503,85 €	10.638,38 €	14%	0,08	0,05	**gained per person**
		Total	681.021,02 €	438.986,15 €		10,58	**6,82**	**64.357,09 €**

Table n. 56: CHEAUL BC model output calculations after variable variation: Time horizon. Source: Own calculations.

The global complication incidence, presented a variation of 11,44%. Following the reasoning presented, the **eleventh hypothesis (H11) was accepted**, proving that this variable has positively influence in the model output, as expected. The correspondent calculations are presented in the table below.

Global complication incidence

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,02111	0,04469	0,02358	0,97	115,00 €	74,13 €	99%	99	0,04	0,03	
I	4,60443	11,12814	6,52371	0,84	161.939,98 €	104.386,51 €	92%	72	7,96	5,13	
II	11,43739	26,40431	14,96692	0,64	376.449,00 €	242.659,03 €	74%	58	15,19	9,79	**Cost per**
III	4,52457	10,09017	5,56561	0,61	321.182,11 €	207.033,99 €	56%	44	4,39	2,83	**QALY**
IV	2,13175	4,72593	2,59418	0,26	36.588,18 €	23.584,74 €	14%	11	0,51	0,33	**per person**
				Total	**896.274,28 €**	577.738,40 €			**28,10**	**18,12**	**31.891,79 €**
			Complication Additional 25%		**976.451,22 €**	629.420,46 €				**18,12**	**34.744,70 €**
			Complication decrease 25%		**876.230,04 €**	564.817,89 €				**18,12**	**31.178,57 €**

Table n. 57: CHEAUL BC model output calculations after variable variation: 25% variation of complication incidence. Source: Own calculations.

This complication calculations that were and will be presented , were made was follows:

	ARF	AHF	APD	ACVE	AA	Ost	AC	AD	Total
Complication Incidence	0,60327	2,77103	2,22670	1,62367	0,61002	0,53528	9,64357	2,19439	20,20794
Total Cost per complication	35.298 €	61.983 €	11.194 €	7.856 €	271 €	11.592 €	8.126 €	2.388 €	
10year model complication cost	21.294 €	171.758 €	24.927 €	12.755 €	165 €	6.205 €	78.365 €	5.239 €	320.708 €
Adicional 25%	26.618 €	214.697 €	31.158 €	15.943 €	206 €	7.756 €	97.956 €	6.549 €	400.885 €
25% Decrease	19.963 €	161.023 €	23.369 €	11.958 €	155 €	5.817 €	73.467 €	4.912 €	300.664 €

Table n. 58: Global complication incidence variation calculations. Source: Own calculations.

Complications	Global 10years therapy Cost	Adicional Complication 25%	Complication Decrease 25%
Total	896.274 €	976.451 €	876.230 €
ARF	896.274 €	901.598 €	894.943 €
AHF	896.274 €	939.214 €	885.539 €
APD	896.274 €	902.506 €	894.716 €
ACVE	896.274 €	899.463 €	895.477 €
AA	896.274 €	896.316 €	896.264 €
Ost	896.274 €	897.825 €	895.886 €
AC	896.274 €	915.865 €	891.376 €
AD	896.274 €	897.584 €	895.947 €

Table n. 59: Total and Individual complication incidence variation calculations. Source: Own calculations.

Please note that we hadn´t considered metastasis incidence (BC direct complication) because this variable is intimately associated with each disease stage progression and therefore, it hasn´t a specific cost or QALY associated. Just BC stages do and those, we add already analyzed.

The ARF complication presented a variation of 0,74%. Following the reasoning presented, the **twelveth hypothesis (H12) was rejected**, proving that this variable has no significant positive influence in the model output, contrary to our expectations. The correspondent calculations are presented in the table below.

ARF complication

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,02111	0,04469	0,02358	0,97	115,00 €	74,13 €	99%	99	0,04	0,03	
I	4,60443	11,12814	6,52371	0,84	161.939,98 €	104.386,51 €	92%	72	7,96	5,13	
II	11,43739	26,40431	14,96692	0,64	376.449,00 €	242.659,03 €	74%	58	15,19	9,79	**Cost per QALY per person**
III	4,52457	10,09017	5,56561	0,61	321.182,11 €	207.033,99 €	56%	44	4,39	2,83	
IV	2,13175	4,72593	2,59418	0,26	36.588,18 €	23.584,74 €	14%	11	0,51	0,33	
				Total	**896.274,28 €**	577.738,40 €			**28,10**	**18,12**	**31.891,79 €**
			Complication Additional 25%		**901.597,85 €**	581.169,97 €				**18,12**	**32.081,22 €**
			Complication decrease 25%		**894.943,39 €**	576.880,51 €				**18,12**	**31.844,44 €**

Table n. 60: CHEAUL BC model output calculations after variable variation: 25% variation of ARF complication.
Source: Own calculations.

The AHF complication presented a variation of 6,06%. Following the reasoning presented, the **thirteenth hypothesis (H13) was accepted**, proving that this variable has a significant influence in the model output, as expected. The correspondent calculations are presented in the table below.

AHF complication

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,02111	0,04469	0,02358	0,97	115,00 €	74,13 €	99%	99	0,04	0,03	
I	4,60443	11,12814	6,52371	0,84	161.939,98 €	104.386,51 €	92%	72	7,96	5,13	
II	11,43739	26,40431	14,96692	0,64	376.449,00 €	242.659,03 €	74%	58	15,19	9,79	**Cost per QALY per person**
III	4,52457	10,09017	5,56561	0,61	321.182,11 €	207.033,99 €	56%	44	4,39	2,83	
IV	2,13175	4,72593	2,59418	0,26	36.588,18 €	23.584,74 €	14%	11	0,51	0,33	
				Total	**896.274,28 €**	577.738,40 €			**28,10**	**18,12**	**31.891,79 €**
			Complication Additional 25%		**939.213,75 €**	605.417,18 €				**18,12**	**33.419,69 €**
			Complication decrease 25%		**885.539,41 €**	570.818,70 €				**18,12**	**31.509,82 €**

Table n. 61: CHEAUL BC model output calculations after variable variation: 25% variation of AHF complication.
Source: Own calculations.

The APD complication presented a variation of 0,87%. Following the reasoning presented, the **fourteenth hypothesis (H14) was rejected**, proving that this variable has not significant positive influence in the model output, contrary to our expectations. The correspondent calculations are presented in the table below.

APD complication

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,02111	0,04469	0,02358	0,97	115,00 €	74,13 €	99%	99	0,04	0,03	
I	4,60443	11,12814	6,52371	0,84	161.939,98 €	104.386,51 €	92%	72	7,96	5,13	
II	11,43739	26,40431	14,96692	0,64	376.449,00 €	242.659,03 €	74%	58	15,19	9,79	**Cost per QALY per person**
III	4,52457	10,09017	5,56561	0,61	321.182,11 €	207.033,99 €	56%	44	4,39	2,83	
IV	2,13175	4,72593	2,59418	0,26	36.588,18 €	23.584,74 €	14%	11	0,51	0,33	
				Total	**896.274,28 €**	577.738,40 €			**28,10**	**18,12**	**31.891,79 €**
			Complication Additional 25%		**902.505,97 €**	581.755,35 €				**18,12**	**32.113,53 €**
			Complication decrease 25%		**894.716,36 €**	576.734,16 €				**18,12**	**31.836,36 €**

Table n. 62: CHEAUL BC model output calculations after variable variation: 25% variation of APD complication.
Source: Own calculations.

The ACVE complication presented a variation of 0,45%. Following the reasoning presented, the **fifthteenth hypothesis (H15) was rejected**, proving that this variable has not significant positive influence in the model output, contrary to our expectations. The correspondent calculations are presented in the table below.

ACVE complication

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,02111	0,04469	0,02358	0,97	115,00 €	74,13 €	99%	99	0,04	0,03	
I	4,60443	11,12814	6,52371	0,84	161.939,98 €	104.386,51 €	92%	72	7,96	5,13	
II	11,43739	26,40431	14,96692	0,64	376.449,00 €	242.659,03 €	74%	58	15,19	9,79	**Cost per QALY per person**
III	4,52457	10,09017	5,56561	0,61	321.182,11 €	207.033,99 €	56%	44	4,39	2,83	
IV	2,13175	4,72593	2,59418	0,26	36.588,18 €	23.584,74 €	14%	11	0,51	0,33	
				Total	**896.274,28 €**	577.738,40 €			**28,10**	**18,12**	**31.891,79 €**
			Complication Additional 25%		**899.462,98 €**	579.793,83 €				**18,12**	**32.005,25 €**
			Complication decrease 25%		**895.477,11 €**	577.224,54 €				**18,12**	**31.863,43 €**

Table n. 63: CHEAUL BC model output calculations after variable variation: 25% variation of ACVE complication.
Source: Own calculations.

The Osteoporosis complication presented a variation of 0,22%. Following the reasoning presented, the **sixteenth hypothesis (H16) was rejected**, proving that this variable has not significant positive influence in the model output, contrary to our expectations. The correspondent calculations are presented in the table below.

Osteoporosis complication

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,02111	0,04469	0,02358	0,97	115,00 €	74,13 €	99%	99	0,04	0,03	
I	4,60443	11,12814	6,52371	0,84	161.939,98 €	104.386,51 €	92%	72	7,96	5,13	
II	11,43739	26,40431	14,96692	0,64	376.449,00 €	242.659,03 €	74%	58	15,19	9,79	**Cost per QALY per person**
III	4,52457	10,09017	5,56561	0,61	321.182,11 €	207.033,99 €	56%	44	4,39	2,83	
IV	2,13175	4,72593	2,59418	0,26	36.588,18 €	23.584,74 €	14%	11	0,51	0,33	
				Total	**896.274,28 €**	577.738,40 €			**28,10**	**18,12**	**31.891,79 €**
			Complication Additional 25%		**897.825,49 €**	578.738,31 €				**18,12**	**31.946,99 €**
			Complication decrease 25%		**895.886,48 €**	577.488,42 €				**18,12**	**31.877,99 €**

Table n. 64: CHEAUL BC model output calculations after variable variation: 25% variation of Osteoporosis complication.
Source: Own calculations.

The Acute Arthralgia complication presented a variation of 0,01%. Following the reasoning presented, the **seventeenth hypothesis (H17) was rejected**, proving that this variable has the least significant positive influence in the model output, contrary to our expectations. The correspondent calculations are presented in the table below.

Acute Arthralgia complication

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,02111	0,04469	0,02358	0,97	115,00 €	74,13 €	99%	99	0,04	0,03	
I	4,60443	11,12814	6,52371	0,84	161.939,98 €	104.386,51 €	92%	72	7,96	5,13	
II	11,43739	26,40431	14,96692	0,64	376.449,00 €	242.659,03 €	74%	58	15,19	9,79	**Cost per QALY per person**
III	4,52457	10,09017	5,56561	0,61	321.182,11 €	207.033,99 €	56%	44	4,39	2,83	
IV	2,13175	4,72593	2,59418	0,26	36.588,18 €	23.584,74 €	14%	11	0,51	0,33	
				Total	**896.274,28 €**	577.738,40 €			**28,10**	**18,12**	**31.891,79 €**
			Complication Additional 25%		**896.315,57 €**	577.765,01 €				**18,12**	**31.893,26 €**
			Complication decrease 25%		**896.263,96 €**	577.731,75 €				**18,12**	**31.891,42 €**

Table n. 65: CHEAUL BC model output calculations after variable variation: 25% variation of acute arthralgia complication.
Source: Own calculations.

The acute cytopenia complication presented a variation of 2,75 %. Following the reasoning presented, the **eighteenth hypothesis (H18) was accepted**, proving that this variable has a significant positive influence in the model output, as expected. The correspondent calculations are presented in the table below.

Acute cytopenia complication

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,02111	0,04469	0,02358	0,97	115,00 €	74,13 €	99%	99	0,04	0,03	
I	4,60443	11,12814	6,52371	0,84	161.939,98 €	104.386,51 €	92%	72	7,96	5,13	
II	11,43739	26,40431	14,96692	0,64	376.449,00 €	242.659,03 €	74%	58	15,19	9,79	**Cost per QALY per person**
III	4,52457	10,09017	5,56561	0,61	321.182,11 €	207.033,99 €	56%	44	4,39	2,83	
IV	2,13175	4,72593	2,59418	0,26	36.588,18 €	23.584,74 €	14%	11	0,51	0,33	
				Total	**896.274,28 €**	577.738,40 €			**28,10**	**18,12**	**31.891,79 €**
			Complication Additional 25%		**915.865,49 €**	590.366,90 €				**18,12**	**32.588,90 €**
			Complication decrease 25%		**891.376,48 €**	574.581,28 €				**18,12**	**31.717,52 €**

Table n. 66: CHEAUL BC model output calculations after variable variation: 25% variation of acute cytopenia complication.

Source: Own calculations.

The acute diarrhea complication presented a variation of 0,18 %. Following the reasoning presented, the **nineteenth hypothesis (H19) was rejected**, proving that this variable don´t have a positive influence in the model output, as expected. The correspondent calculations are presented in the table below.

Acute cytopenia complication

BC Stages	5 years Acumulated Probability	10 years Acumulated Probability	5 to10years Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Costs	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs	
0	0,02111	0,04469	0,02358	0,97	115,00 €	74,13 €	99%	99	0,04	0,03	
I	4,60443	11,12814	6,52371	0,84	161.939,98 €	104.386,51 €	92%	72	7,96	5,13	
II	11,43739	26,40431	14,96692	0,64	376.449,00 €	242.659,03 €	74%	58	15,19	9,79	**Cost per QALY per person**
III	4,52457	10,09017	5,56561	0,61	321.182,11 €	207.033,99 €	56%	44	4,39	2,83	
IV	2,13175	4,72593	2,59418	0,26	36.588,18 €	23.584,74 €	14%	11	0,51	0,33	
				Total	**896.274,28 €**	577.738,40 €			**28,10**	**18,12**	**31.891,79 €**
			Complication Additional 25%		**897.584,08 €**	578.582,70 €				**18,12**	**31.938,40 €**
			Complication decrease 25%		**895.946,83 €**	577.527,33 €				**18,12**	**31.880,14 €**

Table n. 67: CHEAUL BC model output calculations after variable variation: 25% variation of acute diarrhea complication.

Source: Own calculations.

Summarizing the findings previously presented, the model was sensitive to Personal history of disease (0, 1 or 2), Patients age at diagnosis (24-65 or +65), Tumor stage (0, I, II, III and IV), Current treatment drug costs (± 25%), Global BC therapy costs (± 25%), Global BC QALYs ± 25%, Country discount rate (5%/0% or 5%/5%), Study time horizon (5 or 10 years), Global complication incidence (± 25%) and AHF (± 25%), (AC ± 25%), as expected.

The model wasn't sensitive to study perspective, indicating that is consistent whatever the perspective chosen for further analysis; however, contrary to our expectations, the specific ARF (± 25%), APD (± 25%), ACVD (± 25%), AA (± 25%), Osteoporosis (± 25%) and AD (± 25%) previous disease therapy complications hadn´t a significant weight in the model outputs, meaning that the model isn´t sensitive to them, maybe because current drugs used in the standard protocol hadn´t an accumulated toxicity high enough to cause acute events incidence to cause a significant output impact, which are good news.

Therefore, since all the other main model variables (including global complication incidence) were considered to have a strong impact in the model outputs, **we can conclude that the CHEUAL BC model was successfully internally validated.**

As discussed earlier, external validation had not been possible at this time, as well as specific (new) drug sensitivity analysis (that will be analyzed in the next chapter).

Is also important to recall that, if the model costs were overestimated and/or consequences underestimated, the cost-effectiveness ratio **would** be higher; and if the model costs were underestimated and/or consequences overestimated, the ratio would be lower.

4. BRIEF MODEL APPLICATION EXAMPLE

To model application, we simulated the following case study:

A new metastatic breast cancer therapy option of paclitaxel in association with bevacizumab is presented by the pharmaceutical industry to a physitian, as proven to show a huge advance of efficacy in BC stages III and IV and a lot less therapy toxic side effects to the patient. The physician is excited to try this new therapy option, but, in order to do that (following hospitals internal rules) he runs to meeting a schedule with the hospitals´ administration and pharmacy and therapeutical commission, for test authorization. He does his math and states that he can apply this new option to 100 patients within this year. Yet, in the process, he remembers that he was also presented a new "CHEUAL BC model to economic evaluation of medicines" and decides to do some simulation before the request submission. He inserts data in the model of the new drug therapy scheme and obtained the following results:

Current therapy: 120 month therapy cycle

Stages	5 year Probability	10 yea Probability	Utility *per* stage	Cost *per* stage	5% Discounted Cost Per Stage	Utility per Stage	10 Year survival	QALY per patient	5%Discounted QALY
III	3,58	8,07	0,61	255.633,27 €	164.781,21 €	0,61	44	3,55	2,29
IV	1,80	3,91	0,26	30.267,77 €	19.510,61 €	0,26	11	0,43	0,28
				Total	**184.291,81 €**				**2,57**

Table n. 68: CHEAUL BC model application output calculations:current therapy.

Source: Own calculations.

PAC + BEV: 120 month therapy cycle

Stages	5 year Probability	10 yea Probability	Utility *per* stage	Cost *per* stage	5% Discounted Cost Per Stage	Utility per Stage	10 Year survival	QALY per patient	5%Discounted QALY
III	3,09535	7,42373	0,61	263.200,52 €	169.659,06 €	56%	44	1,97	1,27
IV	1,62704	3,69401	0,26	54.859,54 €	35.362,46 €	14%	11	0,10	0,07
				Total	**205.021,52 €**				**1,34**

Table n. 69: CHEAUL BC model application output calculations: new therapy option.

Source: Own calculations.

ICER $_{\text{standard vs. new therapy}}$= (184.291,81 €-205.021,52 €)/(2,57-1,34)= -16.880,56 €/QALY per patient

The oncologist felted wrong. How would he present a new therapy option that had an additional 16.880,56 €/QALY per patient regarding the therapy protocol he was already using? Considering the 100 patients we was willing to apply the new therapy, he estimated an ICER of 1.680.000€/QALY. This was not even a close cost-effectiveness option. In fact it was associated with higher costs and less QALYs for patients… He gave up! This wasn´t definatly a good choice...

Similarly to what structured earlier to current therapy, detailed Model matrix adapted to the new therapy option can be consulted in **Appendix n.12**. The summarizing 20 cycle probability tables are presented below.

	24-64 years Female Gender HER+/ER- No previous History of Complications																					
	Cycle																				Acumul	Acumul
Stages transition	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Total 5years	Total 10years
0	0,00025	0,00025	0,00025	0,00026	0,00026	0,00027	0,00027	0,00027	0,00028	0,00028	0,00029	0,00029	0,00029	0,00030	0,00030	0,00031	0,00031	0,00031	0,00032	0,00032	0,00264	0,00568
I	0,05363	0,05541	0,05719	0,05897	0,06075	0,06253	0,06431	0,06609	0,06787	0,06965	0,07143	0,07321	0,07499	0,07677	0,07855	0,08033	0,08212	0,08390	0,08568	0,08746	0,61640	1,41085
II	0,13432	0,13878	0,14218	0,14661	0,15104	0,15547	0,15989	0,16432	0,16874	0,17317	0,17759	0,18202	0,18645	0,19087	0,19530	0,19972	0,20415	0,20857	0,21300	0,21743	1,53452	3,50962
III	0,03961	0,04007	0,03842	0,03996	0,04289	0,04417	0,04543	0,04668	0,04794	0,04919	0,05045	0,05171	0,05565	0,05692	0,05824	0,05956	0,06088	0,06220	0,06352	0,06484	0,43435	1,01830
IV	0,01820	0,01925	0,02193	0,02200	0,02199	0,02274	0,02338	0,02403	0,02468	0,02533	0,02598	0,02663	0,02597	0,02668	0,02729	0,02791	0,02853	0,02915	0,02977	0,03039	0,22354	0,50182
Death	1,28899	1,33179	1,38327	1,42640	1,46550	1,50844	1,55139	1,59435	1,63730	1,68026	1,72321	1,76616	1,80656	1,84945	1,89234	1,93523	1,97813	2,02102	2,06391	2,10680	14,86768	34,01049

Table n. 70.1: BC Stage Probability Matrix Paclitaxel+Bevacizumab -Oncologist Perspective (Summary). Source: Own production.

	≥ 65 years Female Gender HER+/ER- No previous History of Complications																					
	Cycle																				Acumul	Acumul
Stages transition	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Total 5years	Total 10years
0	0,00025	0,00025	0,00025	0,00026	0,00026	0,00027	0,00027	0,00027	0,00028	0,00028	0,00029	0,00029	0,00029	0,00030	0,00030	0,00031	0,00031	0,00031	0,00032	0,00032	0,00264	0,00568
I	0,05363	0,05541	0,05719	0,05897	0,06075	0,06253	0,06431	0,06609	0,06787	0,06965	0,07143	0,07321	0,07499	0,07677	0,07855	0,08033	0,08029	0,08203	0,31523	0,08012	0,61640	1,62937
II	0,13432	0,13776	0,14219	0,14661	0,15104	0,15547	0,15989	0,16432	0,16874	0,17317	0,17759	0,18202	0,18645	0,19087	0,19530	0,19972	0,19935	0,19030	0,20855	0,21767	1,53350	3,48133
III	0,03961	0,04109	0,03829	0,03997	0,04289	0,03924	0,04579	0,04666	0,04794	0,04919	0,05045	0,05171	0,05565	0,05692	0,05824	0,05956	0,06523	0,06665	0,06750	0,06953	0,43066	1,03209
IV	0,01820	0,01925	0,02205	0,02197	0,02199	0,02274	0,02302	0,02409	0,02468	0,02533	0,02598	0,02663	0,02597	0,02668	0,02729	0,02791	0,02967	0,03031	0,03096	0,03157	0,22332	0,50629
Death	8,79701	9,08907	9,44046	9,73482	10,00160	10,29466	10,58781	10,88097	11,17413	11,46728	11,76044	12,05359	12,32928	12,62197	12,91470	13,20743	13,50197	13,79474	14,08751	14,38028	101,46782	232,11974

Table n. 70.2: BC Stage Probability Matrix Paclitaxel+Bevacizumab -Oncologist Perspective (Summary). Source: Own production.

	24-64 years Female Gender HER+/ER- Previous History of One Complication																					
	Cycle																				Acumul	Acumul
Stages transition	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Total 5years	Total 10years
0	0,00014	0,00014	0,00014	0,00014	0,00014	0,00014	0,00015	0,00015	0,00015	0,00015	0,00015	0,00015	0,00015	0,00016	0,00016	0,00016	0,00016	0,00016	0,00016	0,00016	0,00144	0,00301
I	0,03019	0,03028	0,03128	0,03225	0,03322	0,03419	0,03517	0,03614	0,03711	0,03808	0,03906	0,04003	0,04100	0,04198	0,04295	0,04392	0,04489	0,04587	0,04684	0,04781	0,33791	0,77226
II	0,07562	0,07530	0,07783	0,08025	0,08267	0,08509	0,08751	0,08993	0,09235	0,09477	0,09719	0,09961	0,10203	0,10445	0,10687	0,10929	0,11171	0,11413	0,11655	0,11897	0,84130	1,92210
III	0,02230	0,02372	0,02432	0,02510	0,02697	0,02776	0,02855	0,02935	0,03014	0,03093	0,03172	0,03251	0,03403	0,03480	0,03561	0,03642	0,03723	0,03803	0,03884	0,03965	0,26914	0,62798
IV	0,01025	0,01224	0,01247	0,01285	0,01201	0,01324	0,01354	0,01392	0,01430	0,01467	0,01505	0,01542	0,01541	0,01585	0,01621	0,01658	0,01695	0,01732	0,01769	0,01806	0,12948	0,29403
Death	0,72571	0,76056	0,78220	0,80653	0,82864	0,85291	0,87720	0,90149	0,92578	0,95007	0,97436	0,99865	1,01994	1,04414	1,06836	1,09258	1,11679	1,14101	1,16523	1,18945	8,41109	19,22161

Table n. 70.3: BC Stage Probability Matrix Paclitaxel+Bevacizumab -Oncologist Perspective (Summary). Source: Own production.

	≥ 65 years Female Gender HER+/ER- Previous History of One Complication																					
	Cycle																				Acumul	Acumul
Stages transition	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Total 5years	Total 10years
0	0,00014	0,00014	0,00014	0,00014	0,00014	0,00014	0,00015	0,00015	0,00015	0,00015	0,00015	0,00015	0,00015	0,00016	0,00016	0,00016	0,00016	0,00016	0,00016	0,00016	0,00144	0,00301
I	0,03019	0,03028	0,03128	0,03225	0,03322	0,03419	0,03517	0,03614	0,03711	0,03808	0,03906	0,04003	0,04100	0,04198	0,04295	0,04392	0,04489	0,04587	0,17715	0,04384	0,33791	0,89860
II	0,07562	0,07530	0,07783	0,08025	0,08267	0,08509	0,08751	0,08993	0,09235	0,09477	0,09719	0,09961	0,10203	0,10445	0,10687	0,10929	0,11171	0,10660	0,11692	0,12293	0,84130	1,91889
III	0,02230	0,02372	0,02432	0,02510	0,02697	0,02776	0,02855	0,02935	0,03014	0,03093	0,03172	0,03251	0,03403	0,03480	0,03561	0,03642	0,03723	0,03803	0,03847	0,03969	0,26914	0,62765
IV	0,01025	0,01224	0,01247	0,01285	0,01201	0,01324	0,01354	0,01392	0,01430	0,01467	0,01505	0,01542	0,01541	0,01585	0,01621	0,01658	0,01682	0,01718	0,01755	0,01789	0,12948	0,29346
Death	4,95279	5,19064	5,33830	5,50434	5,65521	5,82087	5,98664	6,15242	6,31820	6,48398	6,64976	6,81554	6,96081	7,12598	7,29126	7,45654	7,62526	7,79061	7,95597	8,12132	57,40340	131,19644

Table n. 70.4: BC Stage Probability Matrix Paclitaxel+Bevacizumab -Oncologist Perspective (Summary). Source: Own production.

	24-64 years Female Gender HER+/ER- Previous History of Two Complications																					
	Cycle																				Acumul	Acumul
Stages transition	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Total 5years	Total 10years
0	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00119	0,00248
I	0,02518	0,02065	0,02245	0,02290	0,02364	0,02432	0,02501	0,02570	0,02639	0,02708	0,02777	0,02846	0,02915	0,02984	0,03053	0,03121	0,03190	0,03259	0,03328	0,03397	0,24334	0,55204
II	0,06306	0,05151	0,05612	0,05721	0,05907	0,06076	0,06249	0,06421	0,06593	0,06765	0,06937	0,07109	0,07282	0,07454	0,07626	0,10098	0,07276	0,08352	0,08251	0,08506	0,60801	1,39693
III	0,01860	0,02274	0,01685	0,02366	0,02640	0,02689	0,02779	0,02850	0,02929	0,03005	0,03083	0,03159	0,03733	0,03663	0,03799	0,03869	0,04654	0,03614	0,04333	0,04134	0,25077	0,63119
IV	0,00855	0,01720	0,01362	0,01202	0,01496	0,01542	0,01572	0,01628	0,01664	0,01713	0,01754	0,01800	0,01629	0,01896	0,01816	0,01914	0,01933	0,02207	0,01814	0,02199	0,14752	0,33714
Death	0,60520	0,68809	0,69795	0,71879	0,72642	0,74695	0,76820	0,78951	0,81081	0,83211	0,85342	0,87472	0,87760	0,89779	0,91861	0,93944	0,96028	0,98112	1,00196	1,02280	7,38402	16,71176

Table n. 70.5: BC Stage Probability Matrix Paclitaxel+Bevacizumab -Oncologist Perspective (Summary). Source: Own production.

	≥ 65 years Female Gender HER+/ER- Previous History of Two Complications																					
	Cycle																				Acumul	Acumul
Stages transition	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Total 5years	Total 10years
0	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00012	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00013	0,00119	0,00248
I	0,02518	0,02065	0,02245	0,02290	0,02364	0,02432	0,02501	0,02570	0,02639	0,02708	0,02777	0,02846	0,02915	0,02984	0,03053	0,03121	0,03106	0,03173	0,03241	0,03308	0,24334	0,54858
II	0,06306	0,05151	0,05612	0,05721	0,05907	0,06076	0,06249	0,06421	0,06593	0,06765	0,06937	0,07109	0,07282	0,07454	0,07626	0,07798	0,07702	0,07868	0,08035	0,08201	0,60801	1,36813
III	0,01860	0,02274	0,01685	0,02366	0,02640	0,02689	0,02779	0,02850	0,02929	0,03005	0,03083	0,03159	0,03733	0,03663	0,03799	0,03869	0,04053	0,04141	0,04229	0,04317	0,25077	0,63124
IV	0,00855	0,01720	0,01362	0,01202	0,01553	0,01514	0,01585	0,01622	0,01667	0,01712	0,01755	0,01799	0,01629	0,01896	0,01816	0,01914	0,02046	0,02090	0,02135	0,02179	0,14791	0,34050
Death	4,13030	4,69604	4,76330	4,90556	4,95761	5,09770	5,24279	5,38816	5,53355	5,67894	5,82433	5,96971	5,98936	6,12719	6,26925	6,41145	6,35897	6,49687	6,63476	6,77265	50,39394	113,24849

Table n. 70.6: BC Stage Probability Matrix Paclitaxel+Bevacizumab -Oncologist Perspective (Summary). Source: Own production.

This specific model application had a purpose. Recently, **bevacizumab** has been approved in combination with chemotherapy (particularly with fluouracilo and leucovorin) for metastatic BC not expressing HER-2 in a lot of countries, either alone or in combination with chemotherapy (Dedes *et al*., 2009) and in different dosage. However, EMEA official drug characteristic summary document (**Appendix 3**), advises its use here tested in the model application; the same reasoning was applied to Paclitaxel, whose most advised reported use in Portugal, by the INFARMED, was described in the official drug characteristic summary document (also in **Appendix 3**).

Apart from the controversial dosage, in Portugal, Bevacizumab is still in stage IV clinical essay, an additional reason why this cost-utility analysis is opportune to the model application test chapter.

The results of the analyses consistently showed that **standard treatment resulted in higher health gain** (increased QALYs) **and less costs than paclitaxel and bevacizumab association.**

However, this chapter is not concluded without the **sensitivity analysis** testing. Remind that there was a missing hypothesis to test, relative to the (new) drug option cost variation, and that now, as we are comparing alternative therapy options, sensitivity analysis result must be given in terms of ICER presented variation.
The results obtained are shown below.

	Drug Cost	Additional 25%	25% Decrease
Paclitaxel	31.733,86 €	39.667,33 €	23.800,40 €
Bevacizumab	87.438,34 €	109.297,93 €	65.578,76 €

Table n. 71: Paclitaxel+Bevacizumab drug costs.

Source: Own calculations.

New option therapy:
120 month therapy cycle Drug Cost -25%

BC Stages	5 years Total Probability	10 years Total Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Cost per Stage	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs
III	3,09535	7,42373	0,61	253.129,06 €	163.166,99 €	56%	44	1,97	1,27
IV	1,62704	3,69401	0,26	44.788,07 €	28.870,39 €	14%	11	0,10	0,07
				Total	192.037,38 €				1,34
				ICER	- 6.307,35 €				

Table n. 72: CHEAUL BC model calculations after variable variation: 25% decrease of (new) therapy drug cost.

Source: Own calculations.

New option therapy:
120 month therapy cycle Drug Cost +25%

BC Stages	5 years Total Probability	10 years Total Probability	Utility *per* stage	Therapy Cost *per* stage	5% Discounted Cost per Stage	5year survival (%)	10 year survival (%)	QALYs per Patient	5% Discounted QALYs
III	3,09535	7,42373	0,61	273.271,99 €	176.151,13 €	56%	44	1,97	1,27
IV	1,62704	3,69401	0,26	64.931,01 €	41.854,53 €	14%	11	0,10	0,07
				Total	218.005,65 €				1,34
				ICER	- 27.453,76 €				

Table n. 73: CHEAUL BC model calculations after variable variation: 25% additional (new) therapy drug cost.

Source: Own calculations.

	Minimum ICER	Maximum ICER	Variation (%)
New drug costs* ± 25%	-6.307,35 €	-27.453,76 €	**335,27**

Table n. 74: BC CHEUAL model one way sensitivity analysis variations results .
Source: Own calculations.

The new drug costs presented a variation of 335,27 %. Following the reasoning presented in the previous chapter, the **second hypothesis (H2) was accepted**, proving that this variable has a significant positive influence in the main model output (ICER), as expected.

As the CHEUAL BC model was previously subjected to one-way sensitivity analysis and was overall considered internally validated, we though there was no purpose for further sensitivity test. We therefore consider this model application also valid.

Summarizing, we can now conclude that hypothesis H2, H3, H4, H5, H6, H7, H8, H9; H10, H11, H13 and H18 were accepted and that the others were rejected.

5. CONCLUSIONS

5.1. THEORETICAL CONCLUSIONS

Novel targeted therapies are now a reality in oncology. The monoclonal antibodies as trastuzumab have proven benefit in both advanced and early stage breast cancers. Furthermore, impressive new technologies such as gene profiling, are becoming major tools for prognostic assessment and prediction of response to certain treatments. Whilst this are certainly good news for patients, it comes at a price. Many of these technologies are very expensive and may result in unprecedented inequalities in the delivery of cancer care. The largest impact may be on developing countries, but inequalities are starting to be felt in some developed nations. Strategies to tackle the resource implications need to be addressed alongside the development of these technologies (Mano, 2006).

Breast cancer is the most frequently diagnosed cancer in women and the second leading cause of cancer mortality. The exact cause of breast cancer is unknown (Radice & Redaelli, 2003). Breast cancer risk is increased in women who have a first-degree relative with the disease. However, only 5–10% of all cases are generally attributed to an inherited genetic mutation.

The incidence of breast cancer increases with age, roughly doubling every 10 years until menopause, when the rate of increase slows down (Radice & Redaelli, 2003).

The prognosis for patients with breast cancer varies widely. In general, the earlier it is detected, the better the prognosis.

Once the presence of cancer has been confirmed, a number of surgical and of radiological procedures are applied and patients categorized through BC stages, based on the extent of tumor involvement and prognostic factors.

The main goal in breast cancer treatment is to eliminate tumor presence, prevent tumor recurrence, and enable patients to live the rest of their lives cancer free. This can be achieved for many patients. However, for patients with advanced disease or recurrence at diagnosis, therapy is designed to inhibit disease progression and to provide palliation, which is the alleviation of the consequence and impact of the disease.

Historically, breast cancer signs and symptoms and adverse effects of the different therapies have been measured based on patient, proxy, nurse and physician reporting. It represents a heavy humanistic burden for patients and their families by significantly disrupting the normal way of life due the physical, emotional, psychological and social involvement required to cope with the disease.

Earlier prognosis and better treatments have contributed to prolong patient life expectancy and have increased the number of long-term survivors. However, the quality of the extended life gained due to the different treatment strategies represents a major issue for the patient and his/her relatives, as well as a major challenge for the future. Accordingly, an increasing amount of attention is being devoted to this expanding patient population (long-term survivors) by the medical communities, and also by healthcare providers and payers due to the potential economic implications (direct patient costs, supportive care, proxies' care and support, loss of productivity, etc.).

It is therefore important that new strategies and treatments are evaluated in terms of cost effectiveness or cost-utility, in order to balance costs incurred against gains attained. This is particularly true in an era of financial constraints, where new therapies are generally more expensive than the existing ones and difficult policy decisions may be needed when adopting such new therapies.

Moreover, in the current context, in which expenditure on medicines continues to increase and the resources available to finance new therapies are limited, it is crucial to make the right decisions, based on the true value of cancer treatments in terms of health benefits, costs and savings for the NHS.

These considerations obviously apply for all types of cancer and other diseases, but especially for a disease as common as breast cancer.

To aid this end, it has been developed the CHEUAL model.

The CHEUAL Breast Cancer Model is a cost-utility analysis simulation model that allows the calculation of long-term health outcomes for patients and economic consequences of implementing different therapeutical interventions in early and metastatic breast cancer. It is able of being adapted to a software, and though to turn interactive, allowing economic evaluations in real time and worldwide (considering

country specific economic parameters), since it can be used in hospital oncology units (by physician and pharmaceutical experts, for clinical decision making), in hospitals´ pharmacy and therapeutics commission (to aid alternative drug inclusion in the hospitals´ formulary decision making) and in healthcare payer organizations (for reimbursement decision making), contemplating the respective perspectives, supporting and turning easier the work of these professionals.

The model integrates 80 semi-Markov decision process matrix for each perspective, with a time horizon of 10 years and was successfully internally validated by one way sensitivity analysis.

Though, **reminding the study objectives previously presented, we can conclude that all have been answered**:

- In fact, we developed and validated a model that allows physicians, pharmacists and reimbursement decision makers to do an economic evaluation of pharmacologic treatment interventions in early stage and metastatic breast cancer, helping them to do their job in a transparent, credible and efficient way (as just described).
- The variables important to include in breast cancer pharmacologic therapy economic evaluation, correspond to the **hypothesis explored who showed that the model output is significantly influenced by them, namely, (new) treatment pattern drug costs, personal history of disease, patient´s age at diagnosis, tumor stage, current treatment pattern drug costs, global therapy cost, global QALY, country discount rate, time horizon of the study, global complication incidence, specific acute hepatic failure and specific acute cytopenia.**
- The economic evaluation technique more adequate to this kind of study is a cost-utility analysis.
- To simulate the progress of breast cancer complications and thought, disease progression we used a Markov decision process matrix.
- Breast cancer incidence in the female Portuguese population country is of 3,24%. Consequence data was collected by published literature, as well as costs of BC stages, considering ambulatory chemo/hormonal and immunotherapy administrated according to each.

- Finally, the model was internally validated through one-way sensitivity analysis and can be used has presented in the model application example.

Although the decision-analysis model employed in this study may appear complex, it represents a considerable simplification of the issues relating to the treatment of breast cancer, allowing investigations geared towards improving the quality of care for breast cancer patients. We hope the information collected will help to optimize health strategies, streamlining and proper sizing available resources, in order to achieve population equity in health.

We started our mission with a model application example of the cost-utility analysis of Paclitaxel in association with Bevacizumab in metastatic BC, option that is actually being studied in the IPOL. Using the CHEUAL model we concluded that this new treatment option corresponds to higher costs and less patient quality adjusted life years, being a less cost-effective option regarding the standard therapy hospital protocol, and that, contrary to the current treatment option, its internal cost per QALY ratio exceeds the willingness-to-pay accepted value.

This points to the CHEUAL BC model as a prototype model that allows the identification of efficient breast cancer management strategies and of treatments for breast cancer that are good value for money in a transparent, credible and efficient way, hopefully starting a new path towards better health resources allocation and public valuation.

5.2. IMPLICATIONS FOR MANAGEMENT

Models are not meant to lead to firm claims about the cost-effectiveness of a drug or technology, rather they serve to reveal the dynamics between inputs and outputs, and aid the understanding of the importance of different factors affecting the results (Annemans, Moeremans & Lamarque, 2008).

In several countries, as a result of patients political pressure, trastuzumab was reimbursed for HER2-positive BC, prior to its evaluation by the EMEA and assessment by the technology appraisal agency. This experience highlights how important economic decisions – such as reimbursement – are taken according to other criteria, thus bypassing information about efficiency. However, pressure to reimburse should not undermine the standard procedure for checking new medicines (that has been instituted to protect the interests of patients). In the future, technology appraisal agencies will be forced to carry out economic evaluations in a shorter time frame (Pen, Priol & Lilliu, 2003). The varied response of technology appraisal agencies to evidence from trials underlines the importance of agreeing on the clinical evidence before starting any economic evaluation. It has also created a situation in which reimbursement of trastuzumab is not equitable between patients in different countries. Therefore, international cooperation between technology appraisal agencies is called for a more uniform assessment of new expensive medicines, highlighting the importance of economic evaluation of medicines.

Submissions for Market Authorization Application for medicines for human use are regulated within the European Union with relevant procedures at community level, in which the value of medicines is considered in terms of efficacy, safety, and pharmaceutical quality. Regarding reimbursement submission, however, individual member States are competent. Other major differences in procedures between submissions for market authorization or reimbursement, relate to criteria for assessment (efficacy and safety vs. additional elements), hypothesis (individual drug benefit/risk ratio vs. [added] value compared to therapeutic alternatives), and comparator (mainly placebo vs. active comparator). According to the *Transparency Directive* however, pricing and reimbursement decisions must be taken in a transparent, objective, and verifiable way with respect of strict timelines (VanWilder & Dupont, 2008).
In Portugal, an economic evaluation study is required to initiate the drug reimbursement request.

Beginning in the late 1980s, many health insurers refused to cover high dose chemotherapy with autonomous bone marrow transplant (HDC/ABMT) for high-risk metastatic breast cancer patients. Insurers denied coverage because there was no

persuasive evidence of clinical effectiveness. In response, many women sued to compel coverage. After years of litigation and the expenditure of approximately $3 billion, randomized clinical trials (RCTs) showed that the procedure was no more effective and possibly more harmful than conventional therapy (Jacobson, Rettig & Aubry, 2007).

Four reasons are outlined for the fact that medicines are by some considered expensive (Almarsdóttir & Traulsen, 2005):

1) there are fundamental differences between medicines and other consumer products;

2) medicines are technology requiring an inordinate amount of research and development;

3) medicines are developed, manufactured, and distributed according to strict regulatory requirements;

4) medicines are most often selected by a physician for a specific patient and reimbursed in whole or in part by a third-party insurer or the state.

According to these authors, pharmaceuticals mean share of GDP has been 1,2% in OECD countries, in recent decades. Pharmaceuticals accounted for 15,4% of total health expenditure, with public spending about half of this amount. Since 1970, the average share of GDP for pharmaceuticals in most countries has increased 1,5% more per year than GDP growth.

Four types of strategies to curb rising pharmaceuticals costs were described and a taxonomy of strategies provided. These were:

1) price and profit controls;

2) reimbursement system charges;

3) other fiscal measures; and

4) quality measures.

Pharmaceuticals policy has suffered from the pervasive misunderstanding that drugs are like any other commodity; resulting in policy makers viewing pharmaceuticals expenditures without thinking about drugs in their proper content of health care. The authors conclude by advocating a balanced approach to policymaking in a environment of rising pharmaceuticals costs.

It has been noted by Guhl (2000) that not all of the cost-containment strategies work according to the intentions of the policy makers. It is therefore important to view these

strategies in context to the health care system in which they are implemented. This is fertile ground for research in pharmaceutical policy, and is very much needed. Researchers and practitioners interested in this area should focus on collecting the evidence base for interventions aimed at curbing rising pharmaceutical costs. This can firstly be done by thoroughly evaluating interventions and disseminating the results to other researchers. Secondly, researchers can collect, analyze and disseminate meta-analyses of such evidence that can be used to build a sound basis for policy makers in the future.

With the CHEUAL BC model, we provide a tool to transparent decision-making, aiding the work of these professionals, as well as doctors, who have a predefined drug budget available to treat their patients and who face proceedings to recover the costs of the prescribed drugs if they exceed their budget sickness funds. On the other hand, the Hospitals´ Pharmacy and Therapeutics Commission faces the decision of which drugs to finance (and include in the hospital´s drugs formulary). These are often costly medicines or methods of treatment currently facing long and difficult negotiations on prices for its products with the Pharmaceutical Industry.

Although the focus is typically put on the bottom line numbers such as a cost-effectiveness ratio or net benefit, understanding the separate cost and benefit components that contribute to the overall results can be even more informative. In this way, economic evaluations could provide a rich source of data to inform decision makers and to aid their understanding of how to shape an intervention for valuable providing. Even if the results of an economic evaluation do not influence whether a policy is adopted, they can help decision-makers to choose among alternative protocols resulting in better informed decisions.
Cost-effectiveness and cost-utility analysis findings should be used as inputs in a deliberative, evidence-based decision making process that considers the viewpoints and values of multiple stakeholders.

5.3. LIMITATIONS AND FUTURE RESEARCH PROPOSALS

Finally, as will become clear from this paper, there is still a lot of room for improvement of the presented and existing models.

A **limitation of all health economic models** is that, because they are based on data from clinical studies, they **do not accurately reflect the real-life situation** were factors as non-compliance and varying standards of care may have an influence.

Other critic that could be argued, is that these **data sources may not be suitable for every population** or setting simulated. There were some doubts about the generalisability of the results of economic evaluations to other cultures and underdeveloped countries. However, few has been written about how the generalisability of studies can be increased (Drummond, 2003).
Note that much of the data needed to construct the CHEUAL matrix had to be collected from international studies, with no proven adequacy to the Portuguese population.

The **results** of analysis models should be interpreted with some caution since they often **depend upon limited clinical data** and they rely upon estimates for many of the parameters involved. Although we attempted to use comparable published trial data, the quality of data is limited by the absence of head to head comparisons of paclitaxel plus bevacizumab and the Portuguese standard therapy protocol (not found in any published reference).

On the other hand**, patients differed across trials** whose data was incorporated in the CHEUAL model. Clinical outcomes were also reported differently. Likewise, inclusion and exclusion trial criteria were different for each literature support.

Again, the literature found **models reviewed interpret and apply the adverse event profiles quite differently**. Some authors only applied the main adverse events, while others applied all adverse events. Some extrapolated the incidence of adverse events beyond the trial duration, while most did not. Some created additional disease stages in their model to account for some adverse events or for withdrawal due to adverse events.

Regardless of how the adverse events are handled in the models, a clear algorithm should be applied based on which adverse events are included, suspected to have a significant impact on treatment costs and on clinical outcomes (Annemans, Moeremans & Lamarque, 2008).

Among the study limitations, it should be mentioned that **some of the studies are developed in EU countries that have used older data**, being therefore **difficult to compare** countries in a therapeutic area such as oncology, where the number of new drugs and procedures is increasing and where the increase in prevalence is also an important factor. We therefore recommend a more updated way to get a more accurate picture of current trends.

However, before modeling systems are accepted, several issues need to be addressed. These issues include **healthcare professionals' acceptance of the technolo**gy, the credibility and validity of the expert system recommendation, the **legal liability** associated with system derived decisions and, most importantly, the economic and personnel resources required for the development and implementation of these systems (Nash, 1994).
In the study of Lessard (2010), it was shown that the impact of economic evaluations on reimbursement decisions has been modest and that results of economic evaluations do not have a good record in predicting funding decisions. This is usually explained in terms of fairness; there is increasing awareness that valuations of QALYs may differ when the QALYs accrue to different patients. The problem, however, is that these equity concerns often remain implicit and therefore frustrate explicitness and transparency in evidence-based decision making. It has been suggested that a so-called equity adjustment procedure may (partially) solve this problem (Stolk *et al.*, 2004).

Regarding **our own model limitations**, remind that the **quantification of costs through GDHs in this study wasn´t possible** because it doesn´t incorporate ambulatory day hospital data (which would turn easier researchers´ and hospital administrators´ work). In the definition of GDHs we also noted that each GDH has a total price for each procedure, including a variety of costs (including medication) without considering the specific consumption of the patient during his hospitalization.

We should also consider when analyzing the **available Portuguese databases** we realize that for some variables, the **most recent estimated data was from the year 2002 and 2005, specially for BC incidence and prevalence data and BC related mortality rate**. Note that since then, the Portuguese mortality derived from cancer had increased, changing the current scenarios in terms of disease burden. This factor associated with increased prevalence of cancer and the aging population will determine an increase in DALYs for cancer. To this end, it will eventually be necessary to conduct further studies, focused on current direct costs of cancer in the Portuguese Health System and heath indicators in the country. This intervention was also claimed in the work of Araújo *et al.* (2009).

Still regarding costs, we discovered that **studies on the costs of treatments are heterogeneous**. **Some studies do not provide information on patients' disease stage**. In some studies, hospital costs include the costs of ambulatory care and in others they do not. Other studies report only the cost of initial therapy and others the cost of terminal care; sometimes they include unspecified periods of time.

We also acknowledged the existence of **considerable variation in costs of breast cancer between Canada, USA and the UK,** that can be mainly explained by differences in the aggressiveness of treatment approach, the nature of the healthcare systems themselves, and the patient populations included in the analyses. However, similarities among the three countries do exist, hospitalization being the major contributor to total cost of treatment, that occurs predominantly in the first year after diagnosis and in the late stage of disease before death.

Trying to find utility measures, we were aware that **patients, as their conditions worsen, tend to be non-compliant with completing questionnaires**. This may generate possible bias (selected populations) and eventually mask the true differences between treatments.

We cannot also forget that the **countries included in our study all have specific guidelines for the application of discount rates** and though, the relationship between the results and the discount rates in each paper is driven by those country-specific requirements.

Regarding specifically the **Markov decision process construction**, there are limitations opportune to describe. The main limitation is that, to fulfill our purpose of given 10 years global probability adequacy for each of the perspectives, we had to develop an **opened matrix**, which **enables us to calculate life expectancy within the different therapy options**; on the other hand, to detail drug toxicities alongside the time they were being administrated, following the standard protocol, we assumed that the first Markov transition cycle corresponded to the first chemotherapy cycle. However, **when we aided additional BC prevalence each six month cycle, we aren´t considering that these will start by the beginning of the therapy** and although these people are subject to the overall toxicities, these are being accounted in fuzzy times regarding the Markov cycle number concerned.

To overcome these gaps, it is advisable that, in future research, the CHEUAL BC model would be **developed also** in **a closed matrix** (although for other purpose); and when considering the opened matrix, to assume the global time horizon toxicity average for each BC stage, making of the Matrix not a decision process matrix, but a Markov chain matrix (as previously discussed).

Relatively to model validation, it is important to **aid further probabilistic sensitivity analysis of the CHEUAL BC model, through the technique of second order Monte Carlo Simulation analysis**, the main used in published references for this purpose.

Furthermore, according to Stahl (2008), when **changing the Markov-cycle duration from one year to six-month, like we have to done to adapt incidence data, one cannot simply divide the calculated transition probabilities by two** to arrive at the appropriate transition probabilities for the shorter cycle. If the original rate is a yearly rate, then the six-monthly probability is

$$p = 1 - ((e\text{-}r)/2)$$

This can be tested in further research, comparing the results of both procedures.

According to Sonnenberg & Beck (1993), **counting probabilities at the beginning of each cycle (as we considered), consistently overestimates survival**. To more accurately reflect the continuous nature of the state transitions, we make the assumption that stage transitions occur, on average, ***halfway through*** each cycle. There is no way to

determine the state membership in the middle of the cycle. However, if we consider the count at the end of each cycle to be in the middle of a cycle that begins halfway through the previous cycle and ends halfway through the subsequent cycle, then the under- and overestimations will be balanced. This is equivalent to shifting all cycles one half cycle to the right. We must then add a half cycle for the starting membership at the beginning to compensate for this shift to the right. The shift to the right makes no difference at the end of the simulation if the cohort is completely absorbed because the state membership at that time is infinitesimal.

However, if the simulation is terminated prior to the absorption of the cohort (like in the CHEUAL model), the shift to the right will result in overestimation of the expected survival. Therefore, for simulations that terminate prior to absorption, an additional correction must be made by subtracting a half cycle for members of the state who are still alive at the end of the simulation. Note that the fundamental matrix representation is equivalent to counting state membership at the ***beginning*** of each cycle. Therefore, the correction that should be applied to the result of a matrix solution is ***subtraction*** of one half cycle from the membership of each starting stage. This will be tested in a future step of the CHEUAL construct.

On the other hand, rate/tax collected from the literature represents the transition at any point in time, while the probability is the proportion that the population is at risk in a specific period in time. That makes the **odds available in the academic literature may not reflect the same time period of the cycle of the Markov model in question.** Data obtained from the academic literature are often expressed as rates ranging from 0 to infinity (mortality rate of 2% per year for illness X), when the odds range from 0 to 1 and have implicit time. One way around this problem in the probability can be done through:

$$P(t)=1-e^{(-rt)}$$

where time is expressed by "t" and the fees for "r" where time is expressed by "t" and the fees for "r".

This means that, if one has only the yearly transition probability and not the rate, the transition probability can be converted to a rate by solving the following equation for "r" ("p" being the year transition probability and "t" the time of the cycle length):

$$r = -\frac{\ln(1 - p)}{t}$$

Then, the calculated rate is used, as above, to recalculate the transition probability (Beck & Pauker, 1983).

Confidence intervals/limits for ICERs can also be constructed using the rectangle method as shown by Walter, Gafni and Birch (2007), which is another challenge towards the future, for the acceptability curve construction threshold calculation.

Model calibration with observational data as previously done in the work of Annemans. Moeremans & Lamarque (2008) could also be done in future research opportunities (as we intend to).

On the other hand, in the course of time, **as new evidence occurs and new insights are generated, the model should be subject to change and actualization**.

It is important to recall that **the model did not take into account treatments received and healthcare costs incurred early in the course of the disease**.
The model also does not take into account the indirect costs associated with advanced breast cancer, not contemplating the society perspective.
In fact, productivity losses incurred by patients with advanced breast cancer are likely to be high and may not be dependent to the chemotherapeutic agent used or the response achieved. In practice, even patients who respond to treatment, experience long term adverse effects, such as peripheral neuropathy and bone pain. Consequently, their work productivity could decline regardless of chemotherapy or response to treatment.
Studies to fulfill these gasps were welcome and certainly important to the country.

As it can be easily understood, **epidemiological surveillance of breast cancer and statistical data are needed** and of utmost importance to provide information for research activities.
In the work of Macedo *et al*. (2008), it has been referred that the amount of quantitative information available regarding this disease, patient profile, treatment and monitoring practices is very low. In order to optimize the implementation of health policies, reliable

and up-to-date information is needed, allowing optimization and balancing of costs and benefits.

We also remind the **importance of finishing the Portuguese study IMPACT**, that has already started and which includes the study of the development of national clinical practice and of epidemiological indicators, the study of country availability and access to innovative drugs and procedures, degree of implementation of these, the consumption of resources and identification of factors that may influence access and quality of care (Macedo *et al.*, 2008).

Summarizing, we consider essential the following research proposals, for further health recovery:

FUTURE ISSUES

1. Cost-effectiveness analysis studies increasingly use probabilistic modeling and multiple thresholds rather than single point estimates, which requires greater sophistication in interpreting results.
2. Additional work on practical methods for calculating quality-adjusted life-years is needed for applications in public health.
3. Acceptable methods to estimate the societal willingness-to-pay for improved health, especially for reductions in morbidity, are needed, including more studies of the monetary valuation of quality-adjusted life-years in different settings.
4. Consideration of the impact of life-saving interventions on future costs must be likely to receive increased attention with population aging.
5. More studies of time costs to individuals and family caregivers and of the potential spillover benefits of improved health to other family members are required to accurately calculate the costs and benefits of health programs, especially in Portugal.
6. Organizations that support evidence-based decision making in public health and health care should sponsor cost-effectiveness and cost-utility analyses as well as research on the valuation of health outcomes to better understand optimal resource allocation.

REFERENCES

1. **ACSS** – Health System Central Administration - Statistical data (2006); (Data on file accessed in 17th July, 2010).

2. Adams, M.; McCall, N.; Orza, M. & Chalmers, T. (1992); *Economic analysis in randomized control trials*; **Medical Care**; Vol. 30; Issue 3; p.231-243.

3. Agnelli, G. & Verso, M. (2007); *Thromboprophylaxis during chemotherapy after advanced cancer*; **Thrombosis Research**; Vol. 120; Suppl. 2, S128–S132.

4. Andronis, L., Barton, P. & Bryan, S. (2009); *Sensitivity analysis in economic evaluation: an audit of NICE current practice and a review of its use and value in decision-making*; **Health Technology Assessment**; Vol.13; Issue 29; p1 – 10.

5. Almarsdóttir, A. & Traulsen, J. (2005); *Cost-containment as part of pharmaceutical policy*; **Pharmaceutical World Science**; Vol. 27; p. 144-148.

6. Annemans, L (2008); *Methodological issues in evaluating cost-effectiveness of adjuvant aromatase inhibitors in early breast cancer – A need for improved modeling to aid decision-making*; **Pharmacoeconomics**; Vol. 26; N.º 5; p. 409-423.

7. Annemans, L; Moeremans, K. & Lamarque, H. (2004); *Health economic assessment of the ATAC trial comparing anastrozole versus tamoxifen in adjuvant treatment of postmenopausal hormone receptor positive early breast cancer*; Poster Presented in the ISPOR 7th Annual European Congress; Hamburg; Germany.

8. Araújo, A.; Barata, F.; Barroso, S.; Cortes, P.; Damasceno, M.; Parreira, A.; Espírito-Santo, J.; Teixeira, E. & Pereira, R. (2009); *Custo do tratamento do cancro em Portugal [Cancer treatment cost in Portugal]*; **Acta Medica Portuguesa**; Vol. 22, p. 525-536.

9. Associação Portuguesa da Doença Inflamatória do Intestino [*Portuguese Association of Inflammatory Bowel Disease*] online: www.apdi.org.pt (accessed in December, 12th, 2010)

10. Banta, H. & Wit, G. (2008); *Public heath service and cost effectiveness analysis*; **Annual Review of Public Health**, Vol. 29; p. 383-397.

11. Barros, J. , Barros, H. & Lunet, N. (2007); *Evolução da mortalidade por cancro da mama em Portugal [Breast cancer mortality evolution in Portugal]*; **Acta Médica Portuguesa**; Vol. 20; p. 139-144.

12. Bates, D.; Su, L.; Yu, D.; Chertow, G.; Seger, D.; Gomes, D.; Dasbach, E. & Platt, R. (2001); *Mortality and costs of acute renal failure associated with amphotericin B therapy*; **Clinical Infectious Disease;** Vol. 32; Issue 5;p.686-93.

13. Beck, J. & Pauker (1983); *The Markov process in medical prognosis*; **Medical Decision Making**; Vol. 3; p.419-458.

14. Berkowitz, N.; Gupta, S. & Silberman, G. (2000); *Estimates of the lifetime direct costs of treatment for metastatic breast cancer*; **Value in Health**; Volume 3; Issue 1; p. 23-30.

15. .Bilici, A.; Ozguroglu, M.; Mihmanli, I.; Turna, H.; Adaletli, I. & Serdengecti, S. (2003); *Nonalcoholic fatty liver disease (NAFLD) associated with breast cancer*; **American Society of Clinical Oncology**; Vol 22.; p.233–241.

16. Block, G.; Putter, H.; Bonnema, E.; Hage, A.; Bartelink, H.; Velde, C. (2009); The *impact of loco-regional recurrences on metastatic progression in early-stage breast cancer: a multistate model;* **Breast Cancer Research and Treatment**; Vol. 117; p. 401-408.

17. Boletim Informativo N.º 4 (2009) – *PNS em foco: doenças oncológicas em Portugal [National Health Plan in focus: oncologic diseases in Portugal]*; **Gabinete de Informação e Prospectiva do Alto Comissariado da Saúde** (GIP/ACS); p. 401–408.

18. Brandle, M. & Herman, W. (2004); The CORE Dia*betes Model*; **Current Medical Research and Opinions**; Vol. 20; Suppl. 1; S1-S3.

19. Brigs, A. & Levy (2006); *Pharmacoeconomics and pharmacoepidemiology – curious bebfellows or a match made in heaven?*; **Pharmacoeconomics**, Vol. 24; Issue 11; p. 1079-1086.

20. Brown, R; Hutton, J. & Burrell, A..(2001); *Cost-effectiveness of treatment options in Advanced Breast Cancer in the UK*; **Pharmacoeconomics**; Vol. 19; N.º 11; p. 1091-1102.

21. Brown, M.; Lipscomb, J. & Snyder, C. (2001); *The burden of illness of cancer: Economic Cost and Quality of Life*; **Annual Review of Public Health**; Vol. 22; p.91-113.

22. Buxton, M. (2006); *Economic evaluation and decision making in the UK*; **Pharmacoeconomics**; Vol. 24; N. 11; p. 1133-1142.

23. Busse, R. (2001) – *Expenditure on health care in the EU: making projections for the future based on the past*; **European Observatory on Health Care Systems; HEPAC**; Vol. 2; p. 158-161.

24. Campbell, J & Ramsey, S. (2009); *The costs of treating breast cancer in the US – A synthesis of published evidence*; **Pharmacoeconomics;** Vol. 27; Issue 3; p.199-209.

25. Capitão, L.; Menezes, J. & Gouveia-Oliveira A. (1996); *"Caracterização epidemiológica da insuficiência venosa crónica em Portugal" [Epidemiological characterization of chronic venous insufficiency in Portugal]*; **Acta Medica Portuguesa**; Vol.9; N. 2-3; p. 69-77.

26. Carrilho, M. & Patrício, L. (2009) *"A situação demográfica recente em Portugal " [A recent Portuguese demographic situation]*, **Revista Estudos Demográficos** n.º 46, pp 59-108, **INE**.

27. Ceia, F.; Fonseca, C.; Mota, T.; Murais, H.; Matias, F.; Costa, C. & Gouveia-Oliveira, A.; *Epidemiologia da insuficiência cardíaca em Portugal continental: Novos dados do estudo EPICA [Epidemiology of heart failure in mainland Portugal: New data from the EPICA study]*; **Revista Portuguesa de Cardiologia**; Vol. 23; pp. 15-22; SUP3.

28. Chabot, I & Rocchi, A. (2010); *How do cost-effectiveness analyses inform reimbursement decisions for oncology medicines in Canada? The example of sunitinib for first-line treatment of metastatic renal cell carcinoma*; **Value in Health**; Vol. 13, Issue 6, p. 837–845.

29. Charlson, M.; Pompei, P.; Ales, K. & MacKenzie C. (1987); *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation*; **Journal of Chronical Disease**; Vol. 40; N.5; p. 373-383.

30. Claxton, K. (2008); *Exploring uncertainty in cost-effectiveness analysis*; **Pharmacoeconomics**; Vol. 26; N 9; p. 781-798.

31. Claxton, K. & Sculpher, M. (2006); *Using value of information analysis to prioritise health research: some lessons from recent UK experience;* **Pharmacoeconomics;** Vol. 24; Issue 11; p.1055-1068.

32. Crivellari, D; Spazzapan, S.; Puglisi, F.; Fratino, L.; Scalone, S. &Veronesi, A. (2010); *Hormone therapy in erlerly breast cancer patients with co-morbidities***; Critical Reviews in Oncology/Hematology**; Vol. 73; p.92-98.

33. Curt, G.; Breitbart, W.; Cella, D.; Groopman, J.; Horning, S.; Itri, L.; Johnson, D.; Miaskowski, C.; Scherr, S.; Portenoy, R. & Vogelzangk, N. (2000); *Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition*; The **Oncologist**; Vol. 5; p. 353-360.

34. D'Agostino, R.; Russell, M.; Huse, D.; Ellison, C.; Silbershatz, H.; Wilson, F.; Hartz, H. (2000); *Primary and subsequent coronary risk appraisal: New results from the Framingham Study*; **American Heart Journal**; Vol. 139, N.º 2, Pt1; p. 272-281.

35. Dedes, K.; Szucs, T.; Imesch, P.; Fedier, A.; Fehr, M. & Fink, D. (2007); *Cost-effectiveness of trastuzumab in the adjuvant treatment of early breast cancer: a model-based analysis of the HERA and FinHer trial*; **Annals of Oncology**; Vol.; p.18: 1493–1499.

36. Dedes, K.; Matter-Walstra, K.; Schwenkglenks, M.; Pestalozzi, B.; Fink, D.; Brauchli, P. & Szucs, T. (2009); *Bevacizumab in combination with paclitaxel for HER-2 negative metastatic breast cancer: An economic evaluation*; **European Journal of Cancer**; Vol. 45; p. 1397-1406.

37. Delea,T.; Smith, R. & Karnon, J. (2002); *Cost-effectiveness of Letrozole versus Tamoxifen as first-line hormonal therapy for postmenopausal women with advanced breast cancer: the US perspective;* **Breast Cancer Research and Treatment;** Vol. 76 (Supplement 1); p. S36-S48.

38. Delea,T.; Karnon, J.; Thomas, S. & Barghout, V. (2005); *Cost-effectiveness of Letrozole versus Tamoxifen as initial adjuvant therapy in hormone receptor-positive postmenopausal women with early breast cancer from US perspective;* Poster presented in the **28th Annual San Antonio Breast Cancer Symposium**, San Antonio.

39. Demers, M; Ho-Tin-Noé, B.; Schatzberg, D.; Yang, G. & Wagner, D. (2011); *Increased efficacy of breast cancer chemotherapy in thrombocytopenic mice*; **Cancer Research**; Accepted for publication in December 15, 2010.

40. Diel, I.; Weide, R.; Köppler, H.; Antras, L.; Smith, M.; Green, J.; Wintfeld, N.; Neary, M. & Duh M. (2009); *Risk of renal impairment after treatment with ibandronate versus zoledronic acid: a retrospective medical records review*; **Support Care Cancer**; Vol. 17; p.719–725.

41. Dranitsaris, G.; Verma, S. & Trudeau, M. (2003); *Cost-utility analysis of first-line hormonal therapy in advanced breast cancer: comparison of two aromatase*

inhibitors to tamoxifen; **Journal of Oncology Pharmaceutical Practice**; Vol.26; p. 289-296.

42. Dranitsaris, G.; Cottrell, W.; Spirovski, B. & Hopkins, S. (2009); *Economic analysis of albumin-bound Paclitaxel for the treatment of metastatic breast cancer*; **Journal of Oncology Pharmaceutical Practice**; Vol.15; p. 67-78.

43. Drummond, M & Stoddart,G. (1984); *Economic analysis and clinical trials*; **Control clinical trials**; Vol. 5; Issue 2; p. 115-128.

44. Drummond, M. (2003); *Making economic evaluations more accessible to health care decision-makers*; **European Journal of Health Economics**; Vol. 4; p. 246-247.

45. **EMEA** (European Medicines Agency – Science Medicines Health) – *European Assessment Reports (EPARs)*; http://www.ema.europa.eu/ema/index.jsp?curl=pages /medicines/human/medicines/000278/human_med_000818.jsp&murl=menus/medicines /medicines.jsp&mid=WC0b01ac058001d124 [accessed in September, 23rd, 2010].

46. Epstein, R.; Leung T.; Mak, J. & Cheung, P. (2006); *Utility of a web-based breast cancer predictive algorithm for adjuvant chemotherapeutic decision making in a multidisciplinary oncology center*; **Cancer Investigation**; Vol. 24; p. 367-373.

47. Fasola, G.; Aita, M.; Marini, L.; Follador, M., Tosolini, M.; Mattioni, L.; Mansutti, M.; Piga, A.; Brusaferro, S. & Aprile, G. (2008); *Drug waste minimization and cost-containment in Medical Oncology: two-year results of a feasibility study*; BMC **Health Service Research**; Vol. 8:p.70.

48. Ferlay, J.; Autier, P.; Boniol, M.; Heanue, M.; Colombet, M. & Boyle, P. (2007); *Estimates of the cancer incidence and mortality in Europe in 2006*; **Annuals of Oncology**; Vol. 18, N. 3; p. 581-592.

49. Formulário Hospitalar Nacional de Medicamentos [*National Hospital Formulary of Medicines*] (2010); **Infarmed**; http://www.infarmed.pt/formulario/frames.php ?fich=if (accessed in Setember, 21st, 2010)

50. Garber, A. & Phelps, C. (1997); *Economic foundations of cost-effectiveness analysis;* **Journal of Health & Economics**; Vol. 16; Issue 1; p. 1-31.

51. Garrison J.; Lubeck, D.; Lalla, D.; Paton, V.; Dueck, A & Perez, E (2007); *Cost-effectiveness analysis of Trastuzumab in the adjuvant setting for treatment of HER 2-positive breast cancer*; **Cancer**; Vol. 110; Issue 3; p. 489-498.

52. **GDHs** – Classificação dos Grupos de Diagnóstico Homogéneos (2006); [Diagnostic classification of homogeneous groups]; http://www.acss.minsaude.pt

/Portals/0/DownloadsPublicacoes/SNS/Info_Actívid/Rel_Nacional_06.pdf [Accessed in July, 15th, 2010].

53. Globocan (2002) – *Female breast cancer EU statistics*; **International Agency on Research on Cancer** (IARC) - European Commission of Health and Consumer Protection, Directorate - Public Health and Risk Assessment.

54. Glynn, D. (2000); *Reimbursement for new health technologies – Breakthrough pharmaceuticals as a 20th Century Challenges*; **Pharmacoeconomics**; Vol. 18; Supplement 1; p. 59-67.

55. Grosse, S.; Teutsch, S. & Haddix, A. (2007); *Lessons from cost-effectiveness research for United States public health policy*; **Annual Review of Public Health**; Vol. 28; p. 365-391.

56. Gudmundsson, G.; Gislason, T.; Lindberg, E.; Hallin, R.; Ulrik, C.; Brøndum, E.; Nieminen, M.; Aine, T.; Bakke, P & Christer Janson (2006); *Mortality in COPD patients discharged from hospital: the role of treatment and co-morbidity*; **Respiratory Research**, Vol. 7; p. 109-119.

57. Guhl (2000); *Pricing and reimbursement systems in Europe*; **Health Economics in Prevention and Care**; Vol. 0; p. 8-10.

58. Herlitz J.; Bang, A. & Karlson, B. (1996); *Mortality, place and mode of death and reinfarction during a period of five years after acute myocardial infarction in diabetic and non diabetic patients*; **Cardiology**; Vol. 87; N.º 5; p.423-428.

59. Hosmer, W.; Malin, J. & Wong, M. (2010); *Development and validation of a prediction model for the risk of developing febrile neutropenia in the first cycle of chemotherapy among elderly patients with breast, lung, colorectal, and prostate cancer*; **Support Care Cancer**; Published online in February, 24th 2010.

60. **IMS Health**, (2006); Statistical data (Data on file, accessed in September, 21st, 2010).

61. **Infarmed** (1998) – *Orientações metodológicas para estudos de avaliação económica de medicamentos – Noembro 1998 [Methodological guidelines for economic evaluation studies of drugs- November, 1998];* Direcção de Avaliação Económica e de Observação do Mercado.

62. **Infarmed** (2009) –*Relatório do consumo de medicamentos em meio hospitalar* - Fevereiro de 2009 *[Report of drug use in hospital environment - February 2009];*

Direcção de Economia do Medicamento e de Produtos de Saúde, Observatório do Medicamento e de Produtos de Saúde.

63. **Infarmed** (2010) – *Resumos das Características dos medicamentos (RCM) [Summaries of Product Characteristics of drugs];* http://www.infarmed.pt/infomed/detalhes.php?med_id=10744&dci=dHJhc3R1enVtYWI=&nome_comer=&dosagem=&forma_farmac=&atc=&estado_aim=&pesquisa_titular=&pagina=1 (accessed September, 23rd, 2010.)

64. **Instituto Nacional de Estatística** (INE) (2009); *Relatório de paridades de poder de compra* 2008 – *Informação à comunicação social de 15 de Dezembro de 2009*; *[Report of Purchasing Power Parities 2008 - Information for media of December 15, 2009]*.

65. Izaks, G.; Westendorp, G. & Knook, D. (1999); *The definition of anemia in older persons*; **Journal of the American Medical Association**; Vol. 281; Issue 18; p.1714-1717.

66. Jacobson, P.; Rettig, R. & Aubry, W. (2007); *Litigating the science of breast cancer treatment*; **Journal of Health Politics – Policy and Law**; Vol. 32; Issue 5; 785-818.

67. Jonsson, B & Wilking, N. (2007); *The burden and cost of cancer.* **Annuals of Oncology**; Vol. 18; Supp 3; p. ii8-ii22.

68. Kabe, K. & Kolesar, J. (2006); *Role of Trastuzumab in adjuvant therapy for locally invasive breast cancer*; **American Journal of Health System Pharmacists**; Vol. 63; p.527-533;

69. Kanis J.; McCloskey, E.; Powles, T.; Paterson, A.; Ashley, S. & Spector, S. (1999); *A high incidence of vertebral fracture in women with breast cancer*; **British Journal of Cancer**; Vol.79; p.1179–81.

70. Karnon, J. (2006); *Aromatase inibitors in breast cancer – A review of cost-considerations and cost-effectiveness*; **Pharmacoeconomics**; Vol. 24; Issue 3;p. 215-232.

71. Karnon, J. & Brown, J. (2002); *Tamoxifen plus chemotherapy versus Tamoxifen Alone as adjuvant therapies for node-positive postmenopausal women with early breast cancer – A stochastic economic evaluation*; **Pharmacoeconomics**; Vol. 24; N.º 3; p. 237-250.

72. Karnon, J. & Jones, T. (2003); *A stochastic economic evaluation of Letrozole versus Tamoxifen as a first-line hormonal therapy – For advanced breast cancer in postmenopausal patients*; **Pharmacoeconomics**; Vol. 21; N.º 7; p. 513-525.

73. Karnon, J.; Johnston, S.; Jones, T. & Glendennig, A. (2003); *A trial-based economic evaluation of letrozole followed by tamoxifen versus tamoxifen followed by letrozole for post-menopausal, advanced breast cancer*; **Annals of Oncology**; Vol. 14; Issue 11; p. 1629-1633.

74. Karnon, J., Delea, T.; Papo, N., Barghout, V.; Thomas, S., & Johnston S. (2005); *Cost-effectiveness analysis of Letrozole versus Tamoxifen as initial adjuvant therapy in hormone-receptor positive post-menopausal women with early breast cancer in the UK*; poster presented in the ISPOR 8th Annual European Congress; Florence, Italy.

75. Karnon, J.; Delea, T.; Johnston, S.; Smith, R.; Brandman, J.; Sung, J.; Goss, P. (2006); *Cost-effectiveness of extended adjuvant Letrozole in postmenopausal women after adjuvant Tamoxifen therapy- The UK perspective*; **Pharmacoeconomics**; Vol. 24; N.º 3; p. 237-250.

76. Keating, G. & Goa, K. (2001); *Management of advanced breast cancer – defining the role of Anastrozole;* **Disease Management Health Outcomes;** Vol. 9; Issue 7; p. 384-402.

77. Kellokumpu-Lehtinen, P.; Bergh, J.; Salminen, E.; Wiklund, T.; Lehtinen, S.; Aronen, P. & Sintonen, H. (2007); *Cost-effectiveness of intensive adjuvant chemotherapy for high-risk breast cancer: Is tailored and dose-escalated chemotherapy with growth factor support (GFS) more costly and less effective than marrow-supported high-dose chemotherapy – results from a randomized study*; **Acta Oncologica**; Vol. 46; p. 146-152.

78. Koroleva, I.; Vel'sher, L.; Kaziulin, A.; Kucheriavyi, I. & Oganesian, T. (2010); *Assessment of gastrointestinal toxicity at patients with breast cancer receiving Taksans chemotherapy and doxorubicin*; **Eksp Klin Gastroenterol**; Issue: 3, pages: 38-43;

79. Kirshner, J.; Hatch, M.; Hennessy, D; Fridman, M. &Tannous, R. (2004); *Anemia in stage II and II breast cancer patients treated with adjuvant doxorrubicin and cyclophosphamide chemotherapy*; **The Oncologist**; Vol. 9; p. 25-32.

80. Konecny, G.; Meng Y.; Untch M.; Wang H.; Bauerfeind I.; Epstein M.; Stieber, P.; Vernes J.; Gutierrez J.; Hong K.; Beryt M.; Hepp H.; Slamon D. & Pegram M. (2004); *Association between HER-2/neu and vascular endothelial growth factor*

expression predicts clinical outcome in primary breast cancer patients; **Clinical Cancer Research;** Vol. 10; Issue 5; p.1706-1716.

81. Kotronen, A; Peltonen, M.; Hakkarainen, A.; Sevastianova, K.; Bergholm, R.; Johansson, L.; Lundbom, N.; Rissanen, A.; Ridderstrale, M.; Groop, L.; Orho-Melander, M. & Yki-Järvinen, H. (2009); *Prediction of non-alcoholic fatty liver disease and liver fat using metabolic and genetic factors*; **Gastroenterology**; Vol. 137; Issue 3; p.865-872.

82. Kuderer, N.; Dale, D.; Crawford, J.; Cosler, L. & Lyman, G. (2006); *Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients*; **Cancer**; Vol. 106; Issue 10; p. 2258-2266.

83. Kurian, A.; Thompson, R.; Gaw, A.; Arai, S., Ortiz, R. & Garber, A. (2007); *Cost-effectiveness analysis of adjuvant Trastuzumab regimens in early HER2/Neu-positive breast cancer*; **Journal of Clinical Oncology**; Vol. 25; N.º 6; p. 634-641.

84. Lamers, L.; Groot, C. & Buijt, I.(2007); *The use of disease-specific outcome measures in cost-utility analysis – The development of Dutch societalpreference weights for the FACT-L Scale*; **Pharmacoeconomics;** Vol. 25; Issue 7; p. 591-603.

85. Lessar, C.; Contandriopoulos, A. & Beaulieu, M. (2010); *The role (or not) of economic evaluation at the micro level: can Bourdieu's theory provide a way forward for clinical decision-making?*; **Social Science and Medicine**; Vol. 70, Issue: 12, p. 1948-56.

86. Lewis, R; Bagnall, M.; Forbes, C.; Shirran, E.; Duffy, S.; Kleijnen, J.; Riemsma, R & Riet, G (2002); *The clinical effectiveness of Trastuzumab for breast cancer: a systemic review*; **Health Technology Assessment**; Vol. 6; Issue 13.

87. Liano, F.; & Pascual, J. (1996); *The Madrid Acute Renal Failure Study Group : Epidemiology of acute renal failure: a prospective, multicenter, community-based study*. **Kidney International**; Vol. 50; p. 811-818.

88. Liberato N.; Marchetti, M. & Barosi, G. (2003); *Clinical and economical issues in the treatment of advanced breast cancer with Biphosphonates*; **Drugs Aging**; Vol 20; Issue 9; p.631-642.

89. Liberato, N.; Marchetti, M. & Barosi, G. (2007); *Cost-effectiveness of adjuvant Trastuzumab in human epidermal growth factor receptor 2-positive Breast Cancer*; **Journal of Clinical Oncology**; Vol. 25; N.º 6; p. 625-633.

90. Lind, P.; Wennberg, B.; Gagliardi, G. & Fornander, T. (2001); *Pulmonary complications following different radiotherapy techniques for breast cancer, and the association to irradiated lung volume and dose;* **Breast Cancer Research and Treatment**; Vol. 68; p.199–210.

91. Lidgren, P.; Jonsson, B.; Redaelli, A. & Radice, D. (2002); *Cost-effectiveness analysis of Exemestane compared with megestrol in Advanced Breast Cancer – A model for Europe and Australia*; **Pharmacoeconomics**; Vol. 20; Issue 2; p. 101-108.

92. Lidgren, P.; Wilking, N.; Jonsson, B. & Rehnberg, C. (2008); *Cost-effectiveness of HER2 testing and Trastuzumab therapy for metastatic breast cancer*; **Acta Oncologica**; Vol. 47; p. 1018-1028.

93. Lidgren, P.; Jonsson, B.; Rehnberg, C.; Wilking, N. & Bergh, J. (2008); *Cost-effectiveness of HER2 testing and 1-year adjuvant Trastuzumab therapy for early breast cancer*; **Annuals of Oncology**; Vol. 19; p. 487-495.

94. Lock, J.; Reinhold, T.; Malinowski, M.; Pratschke, J.; Neuhaus, P. & Stockmann, M. (2009); *The costs of postoperative liver failure and the economic impact of liver function capacity after extended liver resection—a single-center experience*; **Langenbeck's Archives of Surgery**; Vol. 394; Issue 6; p. 1047-1056.

95. Locker,G. (2004); *Cost-utility analysis of anastrozole versus tamoxifen as primary adjuvant therapy in postmenopausal women with early breast cancer from a US healthcare system perspective: the 5-year completed treatment analysis of the ATAC (Arimidex®, Tamoxifen Alone or in Combination) trial*; presented at the **27th Annual San Antonio Breast Cancer Symposium**, San Antonio.

96. Lovrics, P; Cornacchi, S.; Barnabi, F.; Whelan, T. & Goldsmith, C. (2008); *The feasibility and responsiveness of the health utilities index in patients with early-stage breast cancer: A prospective longitudinal study*; **Quality of Life Research**; Vol. 17; p. 333-345.

97. Lundkvist, J.; Wilking, N.; Holmberg, S. & Jonsson, L. (2007); *Cost-effectiveness of Exemestane versus Tamoxifen as adjuvant therapy for early-stage Breast Cancer after 2-3 years treatment with Tamoxifen in Sweden*; **Breast Cancer Research Treatment**; Vol. 102; p. 289-299.

98. Lyman, G.; Lalla, A.; Barron, R. & Dubois, R. (2009); *Cost-effectiveness of Pegfilgrastim versus Filgrastim primary prophylaxis in women with early-stage breast*

cancer receiving chemotherapy in the United States; **Clinical therapeutics**; Vol. 31; Issue 5; 1092-1104.

99. Macedo, A.; Andrade, I.; Moital, I; Moreira, A.; Pimentel, F.; Barroso, S.; Dinis, J.; Afonso, N. & Bonfill, X.(2008); *Perfil da doença oncológica em Portugal: Racional, objectivos e metodologia [Profile of malignant disease in Portugal: Rationale, objectives and methodology]*; **Acta Medica Portuguesa**; Vol. 21: p. 329-334.

100. Macedo, A., Monteiro, I., Andrade, S., Cirrincione, A. & Ray, J. (2010); *Cost-effectiveness of treatment with Tratuzumab in patients with early breast cancer in Portugal*; **Acta Medica Portuguesa**; Vol. 23; Issue 3; p.475-82.

101. Mannan, H. & Koval, J. (2003); *Latent mixed Markov modeling of smoking transitions using Monte Carlo bootstapping*; **Statistical Methods in Medical Research**; Vol. 12; p. 125-146.

102. Mano, M. (2006); *The burden of scientific progress: Growing inequalities in the delivery of cancer care*; **Acta Oncologica**; Vol. 45; p. 84-86.

103. Mansel, R. (2004); *Cost-utility analysis of anastrozole versus tamoxifen as adjuvant therapy in postmenopausal women with early breast cancer; a UK national health service perspective*; presented at the 29th ESMO Congress,Viena, Austria.

104. Mansel, R.; Locker, G.; Fallowfield, L.; Benedict, A. & Jones, D. (2007); *Cost-effectiveness analysis of Anastrozole vs Tamoxifen in adjuvant therapy for early stage breast cancer in the United Kingdom: A 5-year completed treatment analysis of the ATAC (Arimidex, Tamoxifen alone or in combination)*; **British Journal of Cancer**; Vol. 97; p.152-161.

105. Mao, I.; Stricker, C.; Bruner, D.; Xie, S; Bowman, M.; Farrar, John; Brandon, T.; Greene, B. & DeMichele, A. (2009); *Patterns and risk factors associated with aromatase inhibitor-related arthralgia among breast cancer survivors*; **Cancer**; Published online: June 10th, 2009.

106. Martin, S.; Gagnon, D.; Zhang, L.; Bokemeyer, C.; Koody, M. & Hout, B. (2003); *Cost-utility analysis of survival with epoietin-alpha versus placebo in Stage IV Breast Cancer*; **Pharmacoeconomics**, Vol. 21; Issue 16; p.1153 – 1169.

107. McCabe, C.; Claxton, K. & Culyer, A. (2008); *The NICE cost-effectiveness threshold – What it is and what it means*; **Pharmacoeconomics**; Vol. 26; Issue 9; p. 733-744.

108. McKeage, K. & Lyseng-Williamson, K. (2008); *Trastuzumab – A pharmacoeconomic review of its use in early Breast Cancer*; **Pharmacoeconomics**; Vol.26; Issue 8; p.699-719.

109. Metropolis, N. & Ulam, S. (1949); *The Monte Carlo Method*; **Journal of the American Statistical Association**; Vol. 44; Issue 247; p. 335-341.

110. Miles, D.; Chan, A.; Romieu, G.; Dirix, L.; Cortes, J.; Pivot, X.; Tomczak, P.; Taran, T.; Harbeck, N. & Steger, G. (2008); *Randomized, double-blind, placebo-controlled, phase III study of Bevacizumab with Docetaxel or Docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO*; **Journal of Clinical Oncology;** Vol. 26; p. LBA1011.

111. Millar, A. & Millward, M. (2007); *Cost effectiveness of trastuzumab in the adjuvant treatment of early breast cancer: a lifetime model*; **Pharmacoeconomics**, Volume 25, Issue 5, p. 429-442.

112. Miller, K.; Chap, L.; Holmes, F.; Cobleigh, M.; Marcom, P.; Fehrenbacher, L.; Dickler, M.; Overmoyer, B.; Reimann, J.; Sing, A.; Langmuir, V. & Rugo, H. (2005); *Randomized phase III trial of Capecitabine compared with Bevacizumab Plus Capecitabine in patients with previously treated metastatic breast cancer*; **Journal of Clinical Oncology**; Vol. 23; p.792–799.

113. Miller, K.; Wang, M.; Gralow, J.; Dickler, M.; Cobleigh, M.; Perez, E.; Shenkier, T.; Cella, D. & Davidson, N. (2007); *Paclitaxel plus Bevacizumab versus Paclitaxel alone for metastatic breast cancer*; **New England Journal of Medicine**; Vol. 357; p. 2666–2676.

114. Milne, R.; Heaton-Brown, K.; Hansen, P. Thomas, D.; Harvey, V. & Cubit, A. (2006); *Quality of life valuations of advanced breast cancer by New Zealand Women*; **Pharmacoeconomics;** Vol. 24; Issue 3; p.281-292.

115. Miners, A. (2008); *Estimating "costs" for cost-effectiveness analysis;* **Pharmacoeconomics;** Vol. 26; Issue 9; p.745-751.

116. Moreno-Aspitia, A. & Perez, E. (2009); *Anthracycline and/or taxane resistant breast cancer: Results of a literature review to determine the clinical challenges and current treatment trends*; **Clinical Therapeutics**; Volume 31; Issue 9; 1619-1640.

117. Mossialos, E.& Barros, PP. (1998); *Regulação das despesas com medicamentos na União Europeia [Drug expense regulation in the European Union]*- Documento de trabalho 1/98; **Associação Portuguesa de Economia da Saúde** (APES);

118. Munchi, A. (2009); *Resource-sparing and cost-effective strategies in current management of breast cancer*; **Journal of Cancer Research Therapy**; Vol. 5; Issue 2; 116-120.

119. Nash, D.; Windt, P. & Peterson, A. (1994); *Expert-systems – assisting formulary decision-making in the ambulatory setting*; **Pharmacoeconomics**, Vol. 6; Issue 5; p. 478-479;

120. National Health System Hospitals (2005) – *Assistential movement statistics;* http://www.acss.min-saude.pt/Portals/0/DownloadsPublicacoesSNS/ InfoActivid /SN Saúde. pdf [Accessed July, 15th , 2010].

121. Neumam, P. & Sullivan, S. (2006); *Economic evaluation in the US – What is the missing link?*; **Pharmacoeconomics**; Vol.24; Issue 11; p.1163-1168.

122. Neyt, M.; Albrecht, J. & Cocquyt, V. (2006); *An economic evaluation of Herceptin® in adjuvant setting: the Breast Cancer International Research Group 006 Trial*; **Annals of Oncology**; Vol. 17; p. 381-390.

123. Neyt, M.; Huybrechts, M.; Hulstaert, F.; Vrijens, F. & Ramaeckers, D. (2007); *Trastuzumab in Early Stage Breast Cancer: A Cost-effectiveness analysis for Belgium*; **Health Policy**; Vol. 87; p. 146-159.

124. Norum, J. (2000); *Adjuvant cyclophosphamide, methotrexate, fluorouracil (CMF) in breast cancer – Is it cost effective?* **Acta Oncologica**;Vol. 39; Issue 1; p. 33-39.

125. Norum, J. & Holtmon, M. (2005); *Adjuvant fluorouracil, epirrubicin and cyclophosphamide in early breast cancer: Is it cost-effective?*; **Acta Oncologica**; Vol. 44; p.735-741.

126. Norum, J.; Risberg, T. & Olsen, J. (2005); *A monoclonal antibody against HER-2 (Trastuzumab) for metastatic breast cancer: a model-based cost-effectiveness analysis;* **Annals of Oncology**; Vol. 16; p. 909-914.

127. Norum, J.; Olsen, J., Wist, E. & Lonning, P. (2007); *Trastuzumab in adjuvant breast cancer therapy. A model based cost-effectiveness analysis*; **Acta Oncologica**; Vol. 46; Issue 2; p.153-164.

128. Nuijten, M.; Cormick, J.; Waibel, F. & Parison, D. (2007); *Economic evaluation of Letrozole in the treatment of advanced breast cancer in postmenopausal women in Canada*; **Value In Health**; Vol. 3; Issue 1; p. 31-39.

129. **OCDE** - Organisation for Economic Cooperation and development (2004); *Statistic Data for cancer treatment costs 2004*.

130. Odedina, F.; Sullivan, J.; Nash, R. & Clemmons, C. (2002); *Use of pharmacoeconomic data in making hospital formulary decisions*; **American Journal of Health-System Pharmacy**; Vol. 59; N.º 15, p. 1441-1444.

131. Onukwugha, E.; Mullins, C. & DeLisle; S. (2008); *Using cost-rffectiveness analysis to sharpen formulary decision-making: The example of Tiotropium at the Veterans Affairs Health Care System*; **Value in Health**; Vol. 11; Issue 5; p. 980-988.

132. Order N. 19125-B/2010; **Ministers of Economy, Innovation and Development, and Health**; Decree N. 249, Suplement, Serie N. II from 27/12/2010: Approval of Reference Unit Rates of Homogeneous Groups of Drugs, beginning on the 1st of January, 2011.

133. Ordinance No.132/2009, 30th January – **Ministery of Health**; Republic Diary; 1st Serie; N. 21; 2009.

134. Ordinance No. 110A/2007, 23rd January – **Ministery of Heath**; Republic Diary; 1st Serie; N. 16; 2007.

135. Palmer, A.; Roze, S.; Valentine, W.; Minshall, M.; Foos, V.; Lurati, F.; Lammert, M. & Spinas, G. (2004)[a]; *The CORE Diabetes Model: Projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in Diabetes Mellitus (Types 1 and 2) to support clinical and reimbursement decision making*; **Current Medical Research and Opinions**; Vol. 20; Suppl. 1; S5-S26.

136. Palmer, A.; Roze, S.; Valentine, W.; Minshall, M.; Foos, V.; Lurati, F.; Lammert, M. Spinas, G. (2004)[b]; *Validation of the CORE Diabetes Model against epidemiological and clinical studies*; **Current Medical Research and Opinions**; Vol. 20; Suppl. 1; S27-S40.

137. Palmer, A.; Roze, S.; Valentine, W.; Minshall, M.; Foos, V.; Lurati, F.; Lammert, M. Spinas, G. (2004)[c]; *Comparing the long-term cost-effectiveness of Repaglinide plus Metformin versus Nateglinide plus Metformin in Type 2 diabetes*

patients with inadequate glycaemic control: An application of the CORE Diabetes Mode; **Current Medical Research and Opinions**; Vol. 20; Suppl. 1; S41-S51.

138. Paskett, E.; Herndon, J.; Day, J.; Stark, N.; Winer, E.; Grubbs, S.; Pavy, M.; Shapiro, C.; List, M.; Hensley, M.; Naughton, M.; Kornblith, A.; Habin, K.; Fleming, G. & Bittoni, M. (2008); A*pplying a conceptual model for examining health related quality of life in long-term breast cancer survivors: CALGB study 79804*; **Psycho-Oncology**; Vol. 17: p. 1108–1120.

139. Pearson, SA.; Ringland, C.& Ward, R. (2007); *Trastuzumab and metastatic breast cancer: Trastuzumab use in Australia – Monitoring the effect of an expensive medicine access program;* **Journal of Clinical Oncology**; Vol. 25; Issue 24; p. 3688-3693.

140. Pecherstorfer, M.; Rivkin, S.; Body, J.; Diel, I. & Bergstrom, B. (2006); *Long-term safety of intravenous ibandronic acid for up to 4 years in metastatic breast cancer – An open label trial*; **Clinical Drug Investment**; Vol. 26; Issue 6; p. 315-322.

141. Pen, C.; Priol, G. & Lilliu, H. (2003); *What criteria for pharmaceuticals reimbursement? An empirical analysis of the evaluation of "Medical Service Rendered" by reimbursable drugs in France*; **European Journal of Health Economics**; Vol. 4; p. 30-36.

142. Philips, Z; Ginnelly, L.; Sculpher, M.; Claxton, K.; Golder, S. Riemsma, R. Woolacott, N. and Glanville, J. (2004); *Review of guidelines for good practice in decision-analytic modeling in health technology assessment*; **Health Technology Assessment**; Vol. 8; Issue: 36.

143. **Plano Oncológico Nacional** (PON), 2001 *[Oncologic National Plan-2001]* – Conselho Nacional de Oncologia, Resolução do Conselho de Ministros, n.º 129/2001, de 17 de Agosto.

144. **Plano Nacional de Saúde** (PNS) Vol. 1 - Prioridades e Vol. 2, 2004-2010 – *[National Health Plan- Vol. 1 and 2]* Ministério da Saúde.

145. **Plano Nacional de Prevenção e Controlo das Doenças Oncológicas** (PNPCDO) 2007/2010 *[National Plan for Prevention and Control of Cancer Diseases - 2007-2010]*; Ministério da Saúde.

146. Plant, P.; Owen, J.; Parrott, S. & Elliott, M. (2003); *Cost effectiveness of ward based non-invasive ventilation for acute exacerbations of chronic obstructive*

pulmonary disease: economic analysis of randomized controlled trial; **British Medical Journal**; Vol. 326; Issue 7396; p. 956-961.

147. **Portuguese Observatory of Health Systems**: Spring Report of the year 2009.

148. **Portuguese State Budget Report** for 2011.

149. Plosker, G. & Keam, S. (2006); *Trastuzumab – A review of its use in the Management of HER2 – Positive Metastatic and Early Stage Breast Cancer;* **Drugs**; Vol. 66; Issue 4; p. 449-475.

150. Quagari, K.; Karnon, J.; Delea, T.; Talbot, W. & Brandman, J. (2007); *Cost-effectiveness of Letrozole in the extent adjuvant treatment of women with early breast cancer;* **Breast Cancer Research and Treatment**; Vol. 101; p. 37-49.

151. Radice, D. and Redaelli, A (2003)*; Breast cancer management: Quality of life and cost considerations;* **Pharmacoeconomics**; Vol. 21; N. 6; p. 383-396.

152. Ramsey, S.; McIntosh & Sullivan (2001); *Design issues for conducting cost-effectiveness analysis alongside clinical trials*; **Annual Review of Public Health**; Vol. 22; p. 129-141.

153. Rao, S.; Kubisiak, J. & Gilden, D. (2004); *Cost of illness associated with metastatic breast cancer*; **Breast Cancer Research and Treatment**; Vol. 83; p. 25-32.

154. **Rede de Referenciação Hospitalar de Oncologia** (RRHO), 2002 *[Hospital Referral Network of Oncology - 2002]*– Direcção Geral de Saúde, Despacho Ministerial de 17 de Janeiro de 2002.

155. Reed, S. & Schulman, K. (2009); *Cost-utility of sequential adjuvant Tratuzumab for HER2/Neu-positive breast cancer*; **Value in Health**; Volume 12; Issue 5; p.637-640.

156. Reeder, C. & Gordon, D. (2006); *Managing oncology costs*; American **Journal of Management Care**, Vol. 12, p. S3-S16.

157. Rovira, J. (2008); *Transparency of economic evaluations of health technologies*; **Pharmacoeconomics**; Vol. 26; Issue 3; p. 181-183.

158. Rozenberg, S.; Carly, B.; Liebens, F. & Antoine, C. (2009); *Risks of osteoporosis associated with breast cancer treatment: The need to access to preventive treatment*; **Maturitas**; Vol. 64; p. 1–3.

159. Sato, R. & Zouain (2010); *Markov models in health care*; **Einstein**.; Vol. 8 (3 Pt 1); p. 376-379.

160. Sculpher, M. & Drummond, M. (2006); *Analysis sans frontières – Can we ever make economic evaluations generalisable across jurisdictions?* **Pharmacoeconomics;** Vol. 24; Issue 11; p. 1087-1099.

161. Shi, H. & Lyons-Weiler, J. (2007); *Clinical decision modeling system*; **BMC Medical Informatics and Decision Making**; Vol. 7; N.º 3; p. 1-17.

162. Shiroiwa, T.; Fukuda, T.; Shimozuma, K.; Ohashi, Y & Tsutani, K. (2008); *The model-based cost-effectiveness analysis of 1-year adjuvant trastuzumab treatment: based on 2-year follow-up HERA trial data*; **Breast Cancer Research and Treatment**; Vol. 109.; p.559-566.

163. Silva, E. Pinto, C.; Sampaio C.; Pereira, J.; Drummond, M. & Trindade, R. (1998); *Orientações Metodologicas para Estudos de Avaliação Económica de Medicamentos [Mehtodologic Guidelines to Medicines Economic Evaluation Studies]*; **Infarmed**.

164. Simoens, S. (2007); *Economic evaluation and decision making – reimbursing Trastuzumab in early stage breast cancer*; **Pharmacoeconomics**; Vol. 25; Issue 3; p. 181-185.

165. Simpson, D.; Curran, M. & Perry, C. (2004); *Letrozole – A review of its use in postmenopausal women with breast cancer*; **Drugs**; Vol. 64; Issue 11; p.1213-1230.

166. Singer, C.; Kostler, W & Hudelist, G. (2008); *Predicting the efficacy of Trastuzumab-based therapy in Breast Cancer: Current Standards and Future Strategies*; **Biochimia et Biophysica Acta**; Vol. 1786; p. 105-113.

167. Sociedade Portuguesa de Cardiologia [*Portuguese Society of Cardiology*] online: www.spc.pt (accessed in December, 12th, 2010)

168. Sociedade Portuguesa de Hepatologia [*Portuguese Society of Hepathology*] online: www.sphepatologia.pt (accessed in December, 12th, 2010)

169. Sociedade Portuguesa de Nefrologia [*Portuguese Society of Nephrology*] online: www.spnefro.pt (accessed in December, 12th, 2010)

170. Sociedade Portuguesa de Nefrologia [*Portuguese Society of Nephrology*] online: www.spnefro.pt (accessed in December, 12th, 2010)

171. Sociedade Portuguesa de Pneumologia [*Portuguese Society of Pneumology*] online: www.sppneumologia.pt (accessed in December, 12th, 2010)

172. Sonke G.; Beaglehole, S.; Stewart, A.; Jackson, R. & Stewart, F. (1996); *Sex differences in case fatality before and after admission to hospital after acute cardiac events: Analysis of community based coronary heart disease regist*er; **BMJ**; Vol. 313; N.º 7061; p. 853-855.

173. Sonnenberg, F. & Beck, J. (1993); *Markov models in medical decision-making: A pratical guide*; **Medical Decision Making**; Vol.13; p.322-339.

174. Soong, D.; Haj, R. & Leung, M. (2009); *High rate of febrile neutropenia in patients with operable breast cancer receiving Docetaxel and Cyclophosphamide*; **Journal of Clinical Oncology**, Vol 27, N. 26; p.101-102.

175. Stahl, J. (2008); *Modelling methods for pharmacoeconomics and health technology assessment*; **Pharmacoeconomics**; Vol. 26; Issue 2; p. 131-148.

176. Skedgel, C.; Rayson, D. & Younis, T. (2009); *The cost-utility of sequential adjuvant Trastuzumab in women with Her2/neu-positive breast cancer: An analysis based on updated results from the HERA Trial*; **Value In Health**; Vol.12; Issue 3; p. 641-648.

177. Stolk, E.; Donselaar, G.; Brouwer, W & Busschbach, J. (2004); *Reconciliation of economic concerns and health policy*; **Pharmacoeconomics**; Vol. 22; Issue 17; p. 1097-1107;

178. Teerawattananon, Y.; Thavorncharoensap, M. & Mohara, A. (2008); *Measurement of clinical effects*; **Journal of Medical Association of Thailand**; Vol. 91 Suppl 2, p. S38-42.

179. Thompson, D.; Taylor, D.; Montoya, E.; Winer, E.; Jones, S. & Weinstein, M. (2007); *Cost-effectiveness of switching to exemestane after 2 to 3 years of therapy with Tamoxifen in postmenopausal women with early-stage breast cancer*; **Value in Health**; Vol. 10; Issue 5; p. 367-376.

180. Torrance, G. (2006); *Utility measurement in healthcare – the things I never got to*; **Pharmacoeconomics;** Vol. 24; Issue 11; p. 1069-1078.

181. **UK Renal Registry Report** 2002; Bristol.

182. Van Vlaenderen, I.; Canon, J., Cocquyt, V.; Jerusalem, G.; Machiels, J.; Neven, P.; Nechelput, M.; Delabaye, I.; Gyldmark, M. & Annemans, L. (2009); *Trastuzumab treatment of early stage breast cancer is cost-effective from the perspective of the Belgian Health Care Authorities*; **Acta Clinica Belgica**; Vol. 64; Issue; 2; p. 100-12.

183. Vijan, S. (2006); *Should we abandon QALY as a resource allocation tool?* ; **Pharmacoeconomics,** Vol. 24; Issue 10; p. 953-954.

184. Vogel, C.; Silverman, M.; Mansell, P.; Miller, A.; Thompson, J.; Herbick, J; Brunskill, B.; Padgett, D.; McKinney, E. & Sugarbaker, E. (2006); *Mechanisms of levamisole-induced granulocytopenia in breast cancer patients*; **American Journal of Hematology**; Vol. 9, Issue 2, p. 171–183.

185. Walkom, E.; Robertson, J.; Newby, D. & Pillay, T. (2006); *The role of pharmacoeconomics in formulary decision-making - Considerations for hospital and managed care Pharmacy and Therapeutics Committees*; **Formulary**; Vol. 41; p. 374–386.

186. Walter, S.; Gafni, A. & Birch, S. (2007); *Estimation, power and sample size calculations for stochastic cost and effectiveness Analysis*; **Pharmacoeconomics**; Vol. 25; Issue 6; p.455-466.

187. Ward, S.; Pilgrin, H. & Hind, D. (2006); *Trastuzumab for the treatment of primary breast cancer in HER2 positive women: A single technology appraisal*; **School of Health and Related Research**; University of Sheffield; UK.

188. Weinstein, M.; O'Brien, B.; Hornberger, J.; Jackson, J.; Johannesson, M.; McCabe, C. & Luce, B, (2003); *Principles of good practice for decision analytic modeling in health care evaluation: Report of the ISPOR Task Force on Good Research Practices – Modeling Studies*; **Value in Health**, Vol.6, N.º 1; p. 9-17.

189. Weinstein, M. (2006); *Recent developments in decision analytic modelling for economic evaluation*; **Pharmacoeconomics**, Vol. 24; Issue 11; p.1043-1053.

190. Welsing, P; Severens, J.; Hartman, M.; Gestel, A.; Riel, P & Laan, R. (2006); *The initial validation of a Markov model for economic evaluation of (new) treatment for rheumatoid arthristis*; **Pharmacoeconomics**; Vol. 24; Issue 10; p. 1011-1020.

191. Wilder, P. & Dupont, A. (2008); *Introducing evidence-based medicine in reimbursement procedures: Does it affect the outcome?*; **Value in Health**; Vol. 11; N. 4; p. 784-787.

192. Witte, J.; Shivananda, S.; Lennard-Jones, J.; Beltrami, M.; Politi, P.; Bonanomi, A.; Tsianos, E.; Mouzas. I.; Schulz, T.; Monteiro, E.; Clofent, J.; Odes, S.; Limonard, C.; Stockbrügger, R. & Russel MG (2000); *Disease outcome in inflammatory*

bowel disease: mortality, morbidity and therapeutic management of a 796-person inception cohort in the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD); **Scandinavian Journal of Gastroenterology**; Volume 35; Issue 12; p. 1272-1277.

193. Wolfe R.; Ashby, V.; Milford, E.; Ojo, A.; Ettenger, R.; Agodoa, L.; Held, P. & Port, F. (1999); *Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant*; **New England Journal of Medicine**; Vol. 341; N.º 23; p. 1725-1730.

194. Wu, G., Chang, S. & Chen, T.(2008); *A Bayesian random-effects Markov model for tumor progression in women with a family history of breast cancer*; **Biometrics**; Vol. 64; p. 1231–1237.

195. Yelin, E.; Murphy, L.; Cisternas, M.; Foreman, A.; Pasta, D.; Helmick, C. (2007); *Medical care expenditures and earning losses among persons with Arthritis and other rheumatic conditions in 2003, and comparisons with 1997;* ***Arthritis and Rheumatism***; Vol. 56; Issue 5; p. 1397–1407.

196. Yoshiji, H.; Gomez, D.; Shibuya, M. & Thorgeirsson, U. (1996*); Expression of vascular endothelial growth factor, its receptor, and other angiogenic factors in human breast cancer;* **Cancer Research**; Vol. 56; Issue 9; p. 2013-2016.