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A Treatment Decision Model for Breast Cancer Patients

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Abstract

Breast cancer is the most common cancer among women worldwide. While breast cancer screening policies have been widely studied with the goal to achieve early detection, limited research has been done to optimize treatment decisions once a screening policy is established. In this paper, we propose a dynamic decision model to determine optimal breast cancer treatment decisions that consider both the impact of over-treatment and the potential delay in cancer detection. These two failures are caused by spontaneous cancer regression and type II error in mammography results, respectively. Our goal is to maximize a patient's *life score*, which depends on various factors: age, cancer stage, estrogen receptor status, type of treatment and the patient's personal opinion about the side effects. Our results indicate that a treatment decision is not always the best option for a patient, and when the decision is to treat the best treatment decision is not always the same. The optimal treatment policy depends on various factors such as age, personal preferences and cancer stage.

Keywords
Breast cancer, Markov decision process, type II error, screening policies, treatment decisions, cancer regression, mammography, life score

1. INTRODUCTION

Breast cancer is often defined as an uncontrolled growth of breast cells caused by a genetic abnormality. In 2011, the American Cancer Society (ACS) estimated more than 450,000 deaths caused by breast cancer and more than 1,000,000

new cases worldwide (Jemal et al., 2011). The same year, according to the ACS, the lifetime risk of developing invasive breast cancer in female was about 12%.

There are many different types of treatments in practice. According to Cancer Reserach UK (2013), the U.S. Centers for Disease Control and Prevention (CDC) and Senkus et al. (2013), breast cancer treatments are generally composed of a primary treatment and followed by an adjuvant treatment. Primary treatment consists of a surgery that can either remove the whole breast (mastectomy), only the lump area of cancer (lumpectomy) or around a quarter of the breast (quadrantectomy). Adjuvant treatment is done after the surgery in order to remove any undetectable tumour. There are three main types of treatments of this kind: radiotherapy, which uses radiation to destroy cancerous cells; chemotherapy, which uses drugs to destroy cancer cells; hormone therapy, where hormones are induced to the patient and affect the growth of the cells. The effectiveness of the last treatment is limited for patients whose breast cancer is estrogen receptor negative. A combination of those adjuvant treatments can be done for each patient.

The rest of the paper is organized as follows. In section 2, we review medical and operations research literature related to our problem. In section 3 we describe the model for optimal treatment policies. Section 4 present the sources of the model inputs and the estimations. In 5 we present our computational experiments and results. Finally, Section 6 concludes about the performance of the model and present our recommendations and the future work.

2. LITERATURE REVIEW

This section presents a summary of literature references considered relevant for purposes of this study. First, we review research regarding cancer regression and imperfection in mammography results. Finally, studies concerning treatment policies are presented.

2.1. Cancer Regression & Type II Error in Mammography Results

Vargas et al. (2014) made a literature review about both topics. They establish that cancer regression does exists from the in situ stage, and solved a Markov decision process in order to determine at what age a woman with breast cancer should be treated or not. Their results consisted on doing less treatment decisions when cancer regression is considered in order to avoid the effects of over-treatment. They also considered type II error in mammography results, which implies that a woman with breast cancer is diagnosed as a cancer free patient. In this case, the treatment decisions increase because of the potential delay in cancer detection.

2.2. Treatment Decision Process

Breast cancer treatments are usually composed of a combination of a surgery and an adjuvant treatment (Senkus et al., 2013). This means that there are too many different combinations of one of the possible surgeries and some of the possible adjuvant treatments. Having more treatment decisions to choose, the quality and quantity of the remaining life of the patient can be improved because a more personalized treatment for an specific patient can be done.

Also, many cancer patients wish to be active participants in the medical decision process. Usually, patients are not being well informed about their disease and treatment options: in an study made by Gattellari et al. (1999) found that the impact of the treatment on the quality of life was discussed with only 36% of the patients, while only 58% were told about their life expectancy. Leighl et al. (2004) implemented Decision Aids to help patients to make specific and difficult choices among options by providing information on the options and outcomes. This resulted in a potentially improving on the patients' well being.

One study that includes the different treatment options in cancer patients and the patient's participation in the decision process was made by (Simon, 2009). The objective was to find the best decision for a patient with prostate cancer considering five possible options: surgery, external radiation, seed radiation, dual radiation and no treatment. Two main factors were

critical in the treatment decision: quantify the probabilities of death and side effects over time and incorporate the patient's individual preferences into the analysis. The methodology included the introduction of *life score*, that is a measure of the quantity and quality of life for a specific patient. In the study, a patient was evaluated using the methodology and the model recommended him to do surgery.

3. METHODOLOGY

This section is devoted to describe our model for optimal breast cancer treatment. Details of the model formulation and sources of input data are presented.

3.1. Model Formulation

In order to find the optimal treatment policy for breast cancer that considers the medical facts discussed in Section 2.1 and Section 2.2, we formulate a discrete-time, finite-horizon Markov decision process (MDP) model based on the work of Vargas et al. (2014). The objective is to maximize the total expected life score of a patient, considering both the remaining life years and the quality of life of the patient. We model the natural history of breast cancer using a discrete-time Markov chain with the following four states as presented in Figure 1: cancer-free, in situ cancer, invasive cancer and death. Spontaneous breast cancer regression is considered only from in situ cancer.

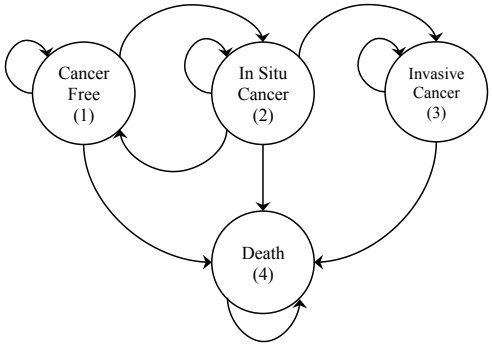

Figure 1. Four-state discrete-time Markov chain for breast cancer natural history

We assume that whenever the observed state of a patient is cancer free, the decision that will be made is not to treat. For the in situ and invasive cases, the possible decisions include different combinations based on the ESMO Clinical Practice Guidelines (Senkus et al., 2013). Our model not only considers treatment, but it also evaluates the possibility of waiting. This assumption differs from other existing models and is based on the inclusion of cancer regression as an established medical fact and the concerns that patients may have about the side effects of treatment.

It is worth mentioning that our model does not include type I error in mammography results (false positive results), since biopsy tests are used to confirm the presence of the disease. On the contrary, type II error is included in the model and hence a negative result does not necessarily imply that the patient is healthy.

Given all the particularities above, we define the MDP model with the following components:

- *Set of decision epochs* $\Upsilon = \{40, 41, 42, ..., 100\}$. We adopt the ACS screening recommendation that a woman should receive annual mammography screening from the age of 40 (Smith et al., 2010). We define the upper boundary of life as 100 years in accordance with the maximum life span reported in the United States Life Table for 2012 (Arias, 2012).
- *State space* $S = \{1, 2, 3, 4\}$, where the cancer state of a patient at decision epoch t is defined as $s_t \in S \quad \forall\, t \in \Upsilon$. In particular, 1 represents a cancer-free patient, 2 represents a patient with in situ (non-invasive) cancer, 3 represents a patient with invasive cancer and 4 represents a death state.

- *Post-diagnosis cancer distribution* is denoted by $Q_t(S)\ \forall\ t \in \Upsilon$. We define the *post-diagnosis cancer distribution* as a discrete probability distribution over all elements of S once the diagnosis procedure is finished. The element q_s^t represents the probability that the state of a patient is s at decision epoch t after the patient has undergone a mammogram or both a mammogram and a biopsy test, and therefore, $Q_t(S) = \{q_s^t : s \in S\}$. Vargas et al. (2014) proposed a methodology to obtain and include the post-diagnosis cancer distribution in the MDP model.
- *Observed cancer state space* $\Omega = \{1,2,3\}$. After the diagnosis procedure is finished the observed cancer state $o_t\ \forall\, t \in \Upsilon$ can be healthy (1), with in situ cancer (2) or invasive cancer (3). Since we do not consider type I error, the observed and the real cancer states are the same when malignant cells are present in a patient. On the contrary, when the observed cancer state is healthy we use the post-diagnosis cancer distribution to describe the real cancer state of a patient.
- *Action Space* $A(s)$ depends on the cancer stage of the patient and her hormone receptor status. If the patient is observed as cancer free, then the only possible decision is not to treat. Otherwise, the patient goes through the biopsy test to identify her cancer stage. In that case, the treatments usually consist on combinations of a primary treatment and some adjuvant treatments. Figure 2 presents the decision making process of our model.

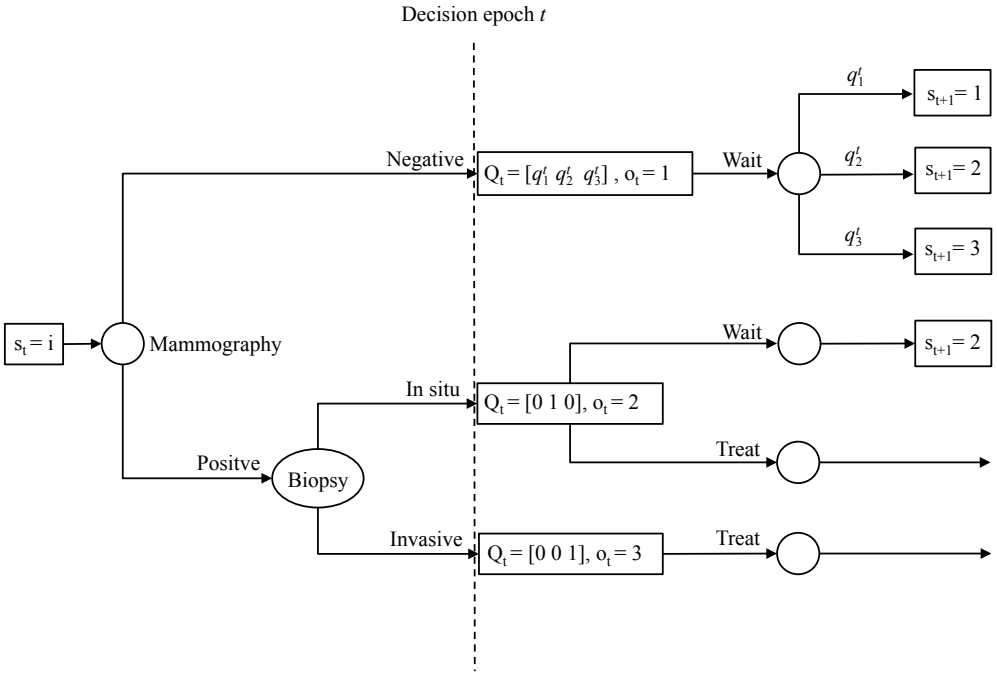

Figure 2. Decision making process for breast cancer treatment

According to Senkus et al. (2013), a surgery is always recommended when the cancer is confirmed present. It could be either a breast conserving surgery (lumpectomy or quadrantectomy) or a mastectomy, when the whole breast is removed. After a surgery is done, the adjuvant treatment is applied. For in situ cancers radiation therapy is recommended, but is not necessary if the patient has low risk or a mastectomy was done before. On the other hand, for invasive cancers radiotherapy is also strongly recommended after a breast conserving surgery. After a mastectomy, radiation therapy is recommended for invasive cancer patients with positive deep margins and four or more positive axillary nodes. Chemotherapy is strongly recommended for invasive cancers no matter which primary treatment had been done. Finally, if a patient is estrogen receptor positive, hormone therapy is also recommended. From this information the possible decisions can be obtained. Table 1 shows all the possible actions for each state of the patient. No treatment decision is also available for all the possible states of the patient in order to consider the possibility to avoid the impact of over treatment and to consider spontaneous cancer regression from the in situ stage.

Table 1: Possible treatment decisions for breast cancer patients.

State	Decision	Treatment
All	1	No treatment
In situ	2	M
	3	BCS
	4	BCS+RT
	5	M+HT
	6	BCS+HT
	7	BCS+RT+HT
Invasive	8	M+CT
	9	M+RT+CT
	10	BCS+RT+CT
	11	M+CT+HT
	12	M+RT+CT+HT
	13	BCS+RT+CT+HT

Build from (Senkus et al., 2013) and considering no treatment decision in all states. M: Mastectomy, BCS: Breast Conserving Surgery, RT: Radiation Therapy, CT: Chemotherapy, HT: Hormone Therapy.

It is also important to note that if the cancer of the patient is estrogen receptor negative, the actions 5, 6, 7, 11, 12 and 13 are not considered because they imply that the treatment of hormone therapy is effective.

- *Transition probability matrices* $P(a_t)\ \forall\ t \in \Upsilon$. Let a_t be the age group of the patient, that is the 5-year age interval of a patient beginning from age 40, then $p_{ij}(a_t)$ is the probability that a patient in age group a_t goes from state i to state j in one year, $i, j = 1,2,3,4$. The natural progression transition matrix is presented in Equation 1. Note that the death state includes both death from another cause and death from breast cancer. The last one is only possible to be done from the invasive cancer state. We assume only invasive cancer patients will die from breast cancer.

$$P(a_t) = \begin{pmatrix} p_{11}(a_t) & p_{12}(a_t) & 0 & p_{14}(a_t) \\ 0 & p_{22}(a_t) & p_{23}(a_t) & p_{24}(a_t) \\ 0 & 0 & p_{33}(a_t) & p_{34}(a_t) \\ 0 & 0 & 0 & 1 \end{pmatrix} \tag{1}$$

The matrices were build in a similar way as in Maillart et al. (2008). The methodology is presented in Section 4.2. No study in the literature models natural progression differently for estrogen receptor positive and negative, so we assumed that the matrices work for both of them.

In order to represent cancer regression, we use an analytical methodology presented by Zhang and Ivy (2012a) and that Vargas et al. (2014) implemented. They proposed the following modification to the original matrix to allow a positive probability that the patient will move from a in situ cancer state to a cancer free state.

$$P^*(a_t) = \begin{pmatrix} p_{11}(a_t) & p_{12}(a_t) & 0 & p_{14}(a_t) \\ p_{21}(a_t) & p^*_{22}(a_t) & p^*_{23}(a_t) & p_{24}(a_t) \\ 0 & 0 & p_{33}(a_t) & p_{34}(a_t) \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

$$p_{21}(a_t) = u \cdot p_{22}(a_t) + v \cdot p_{23}(a_t)$$
$$p^*_{22}(a_t) = (1-u) \cdot p_{22}(a_t)$$
$$p^*_{23}(a_t) = (1-v) \cdot p_{23}(a_t)$$
$$0 \leq u, v \leq 1$$

where u and v are fractions of the self-loop and the progression transition probabilities respectively; these proportions are used to extract information from the existing probabilities and build the regression transition.

- *Discount factor* λ. We select a discount factor of 0.97 that has been previously used in dynamic decisions models regarding medical treatment (Chhatwal et al., 2010).
- *Immediate rewards* $r_t(s,a)\ \forall\ s \in S,\ a \in A(s),\ t \in \Upsilon$. The rewards of this model should consider both the remaining length of life of the patient until the next decision epoch and the quality of life of that period of time. The value of the rewards is a function of the patient cancer state and her corresponding treatment, so it would be possible to compare the different treatment options. Also, the immediate rewards should consider how each of the side effects of the treatment affects the woman's life. As it was mentioned before, quality of life is a subjective measure implying that patient's participation in the decision process should be included in the rewards' estimation.

  The goal of the rewards is to consider the remaining life years of the patient and how each of the side effects caused by treatment specifically affects her quality of life. This means that the values of the rewards are different between women and thus the methodology should consider the woman's personal opinion about how the side effects would affect her life. Simon (2009) implemented the life score metric in the development of the Prostate Cancer Decision Analyst (PCaDA) website. Based on that concept we define Equation 2 as the life score of our problem. When the decision is to treat, the life score corresponding to the treatment is considered as the immediate reward $r_t(s,a)\,,\ a \neq 1$.

$$\begin{aligned} \textit{Life Score} = & \\ & \int_{CurAge}^{MaxAge} f(\textit{LifeSpan} = x)\cdot \\ & \left(\int_{CurAge}^{x} P(\textit{No Death from Cancer at Time} = t)\cdot \right. \\ & \left. \prod_{i \in \textit{Side Effects}} (1 - P(\textit{Side Effect } i \textit{ at Time} = t)\cdot(\textit{Side Effect } i EW))\, dt \right) dx \end{aligned} \tag{2}$$

In the equation, $f(\textit{LifeSpan} = x)$ is the probability density function for the patient's length of life before considering breast cancer. $P(\textit{No Death from Cancer at Time} = t)$ is the probability that the patient has not died from breast cancer at time t, assuming that the patient has not died from any other cause at or before time t. $P(\textit{Side Effect } i \textit{ at Time} = t)$ is the probability that the patient has the side effect i at time t, acquired from any of the treatment (or not treatment) options. Finally $(\textit{Side Effect } i EW)$ is the emotional weight that the patient assigns to the side effect i. A detailed explanation of the estimation of each element is presented in Section 3.2.

It is also important to note that the life score is a number that considers the remaining life years of the patient, meaning that if a treatment is chosen, the patient cannot take any other decision later. On the other hand, if the patient chooses not to treat, the immediate reward is the one-year life score as presented in Equation 3. In that case, another decision can be done in the next screening period.

$$\begin{aligned} r_t(s,1) = & P(\textit{No Death from Cancer at Time} = t)\cdot \\ & \prod_{i \in \textit{Side Effects}} (1 - P(\textit{No Treatment Side Effect } i \textit{ at Time} = t)\cdot(\textit{Side Effect } i EW)) \end{aligned} \tag{3}$$

3.2. Life Score Estimation

We introduce each element for the life score calculation presented in Equation 2. Table 2 summarizes the sources of data input for each element of the life score.

Table 2: Data sources of the elements of the life score.

Item	Source
$f(LifeSpan = x)$	CDC et al. (2011)
	SEER (2010)
$P(No\ Death\ from\ Cancer\ at\ Time = t)$	Hwang (2009)
	Tabar et al. (2000)
	Bloom et al. (1962)
	Senkus et al. (2013)
Side Effects Definition	Hassey Dow et al. (1996)
$P(Cancer\ Recurrence\ at\ Time = t)$	Lawrence (2009)
	Silverstein (2009)
	Clarke et al. (2005)
	Fisher et al. (2002)
	Senkus et al. (2013)
$P(Change\ in\ Appearance\ at\ Time = t)$	ACS (2014)
$P(Fatigue\ at\ Time = t)$	Lerdal et al. (2005)
	Bower et al. (2006)
$P(General\ Pain\ at\ Time = t)$	Clarke et al. (2005)
	Senkus et al. (2013)

$f(\boldsymbol{LifeSpan} = x)$ In order to estimate the probability density function of the life time of a woman without breast cancer $f(LifeSpan = x)$ was approximated to a 1-year discrete function. Hence, the probabilities found to build the transition matrices can be used, specifically the $p_{14}(a_t)$ values. That is, the 1-year probability of dying from another cause different from breast cancer at the age group a_t, or in other words, the probability that a woman without breast cancer dies given her age.

This suggests that the probability that a woman lives until an age x is the probability that she survived until age $x-1$ times the probability that she dies at x by a cause other than breast cancer. Mathematically, $f'(x) = p_{14}(x)\prod_{i=0}^{x-1}(1 - CDC\ mortality\ rate(i))$. The value of the $CDC\ mortality\ rate(i)$ was obtained from the CDC statistic results (2009), and it includes any type of death cause.

It is important to note that the sum of $f'(x)$ over all x values is not 1 because the probabilities $p_{14}(x)$ and the *CDC mortality rate*(i) were obtained as death rates from the CDC statistic results (2009) and the SEER breast cancer mortality rate (1975-2010). They are not probability functions, and thus a normalization of $f'(x)$ is conducted as shown in Equation 4.

$$f(LifeSpan = x) = f(x) = \frac{f'(x)}{\sum_{i=0}^{MaxAge} f'(i)} \tag{4}$$

$P(\boldsymbol{No\ Death\ from\ Cancer\ at\ Time} = t)$ It is the probability that given the patient cancer state and treatment, she does not die from breast cancer by time t. Let $P(No\ Death\ from\ Cancer\ at\ Year = i)$ be the probability that a patient of age i survives from cancer for one year. In that case, Equation 5 shows the relationship between both probabilities.

$$P(No\ Death\ from\ Cancer\ at\ Time = t) = \prod_{i=CurAge}^{t} P(No\ Death\ from\ Cancer\ at\ Year = i) \tag{5}$$

- *Cancer free:* This probability is assumed to be 1 for the remaining years of the patient. If the patient develops cancer, then the state of the patient will be different (in situ or invasive) so this probability would change.
- *In situ:* In the case when the patient is in an in situ state, the long term cause specific survival is 99% when a mastectomy or a lumpectomy is done (Hwang, 2009). It was assumed that if the patient chooses one of the two surgical treatments she

will not die from breast cancer. Hence $P(\textit{No Death from Cancer at Year} = i) = 1 \, \forall t = 0, ..., 100$ if a breast conserving surgery or mastectomy is done when the patient is in the in-situ stage.

If the treatment of an in-situ stage patient does not involve any surgical intervention, then the probability that the patient survives from cancer for one year is showed in Equation 6. That is, the complement of the probability of dying from breast cancer at year i. This last probability is computed as the probability of advancing into an invasive state in 6 months and then multiply it by the probability of dying from breast cancer in 6 months. The first one is estimated using mean sojourn time (Tabar et al., 2000) of patients and times two in order to get a 6-month probability. The second term is the complement of surviving 6 months with invasive cancer. That is, the complement of Bloom et al. (1962) proportion of survivals in three years to the power of $1/6$.

$$\begin{aligned} &P(\textit{No Death from Cancer at Year} = i | \textit{In situ cancer, No surgical treatment}) \\ &= 1 - \frac{1}{\textit{Tabar MST}(i) \times 2} (1 - \textit{Bloom's three year untreated survival } (i))^{1/6} \end{aligned} \tag{6}$$

- *Invasive:* If no surgery is done, then the probability of not dying from breast cancer is considered as the natural progression of cancer, as shown in Equation 7. It is Bloom et al. (1962) proportion of survivals in three years to the power of $1/3$ in order to have the one-year survival probability.

$$\begin{aligned} &P(\textit{No Death from Cancer at Year} = i | \textit{Invasive cancer, No surgical treatment}) \\ &= \textit{Bloom's three year untreated survival } (i)^{1/3} \end{aligned} \tag{7}$$

According to Senkus et al. (2013), there is a 50% of risk reduction if a surgery and a radiotherapy is performed. Given that all the possible treatment options for invasive cancer consider at least one adjuvant treatment, we will assume that a 50% of risk reduction is applied if the patient goes through surgery, as shown in Equation 8.

$$\begin{aligned} &P(\textit{No Death from Cancer at Year} = i | \textit{Invasive cancer, Surgical treatment}) \\ &= 1 - (1 - \textit{Bloom's three year untreated survival } (i)^{1/3}) \times 0.5 \end{aligned} \tag{8}$$

$P(\textbf{\textit{Side Effect } i \textit{ at Time}} = t)$ We define the main side effects of the treatments based on an early study by Hassey Dow et al. (1996), which estimated long-term quality of life of 294 breast cancer survivors. In their study, they analyzed four main aspects: physical wellbeing, psychological wellbeing, social wellbeing and spiritual wellbeing. They concluded that physical changes such as fatigue, aches and pains deserve more attention among long term survivors of breast cancer. Psychologically, distress associated with initial diagnosis and treatment had the worst outcomes, and also fears over recurrent, metastatic and second cancers greatly affect quality of life, followed by a change in appearance. Family distress and financial burden had the worst outcomes of social wellbeing.

We considered four side effects from Hassey Dow et al. (1996) study: cancer recurrence, change in appearance, fatigue and general pain (nausea, constipation, sleep problems). How to estimate the probability of having each of these side effects is explained below.

- Cancer Recurrence

  Cancer free: The probability of having recurrence for cancer free patients is zero for all decision epochs.

In situ: According to Lawrence (2009), the 12 year recurrence probability of a patient with in situ cancer that undergoes only breast conserving surgery is 32.9%. In addition, Silverstein (2009) estimated that the 12-year recurrence probability is between 1% and 4% when a mastectomy is done. We consider the mean value of 2.5%. For both cases, the probability of having recurrence in a year t is the cumulative probability of a geometric distribution where the cumulative probability at 12 years is 32.9% and 2.5% for the breast conserving surgery and mastectomy cases, respectively, starting from the age of the patient until the following 12 years. In other words, each year a patient has a probability p_{rec} of having recurrence. In that order of ideas, $\sum_{i=1}^{12}(1-p_{rec})^{i-1}p_{rec} = 32.9\%$ for the case of breast conserving surgery. We assume that after 12 years upon treatment of possible recurrence the probability of a recurrence is 0%.
The effects of the adjuvant treatments are mentioned in Lawrence (2009) and Clarke et al. (2005). Radiation therapy has a $1/2$ reduction on cancer recurrence while hormone therapy has a reduction of 26.2%. This applies to all the 12 years following treatment when the risk of recurrence is present.
Finally, if the decision is not to treat, the probability of having recurrence at time t is $1 - \textit{Regression Probability}$ for the remaining years of the patient, where the *Regression Probability* is the average probability of going back from the in situ stage to the cancer free stage $(p_{21}(a_t))$.

Invasive: Fisher et al. (2002) found that the 20-year recurrence probability of a patient that was treated with breast conserving surgery and with mastectomy were 42.4% and 37.2%, respectively. Similar to the in situ case, a geometric distribution is used to model this situation. If a radiation therapy is used, a reduction of $2/3$ on cancer recurrence is done when the primary treatment is breast conserving surgery (Senkus et al., 2013). Due to lack of information, the same proportion of reduction is assumed if the primary treatment is mastectomy. On the other hand, in the study of Clarke et al. (2005) the average reduction on recurrence were 26.2% and 15.5% if hormone therapy and chemotherapy were implemented, respectively. Finally, if a no treatment decision was done, the probability of having recurrence is 1 for the remaining living years of the patient.

- Appearance

  This side effect is affected only by the primary treatment of breast cancer. We assume that skin changes or other appearance side effects produced by adjuvant treatment can be ignored as compared with the changes in the body due to surgery. Equation 9 summarizes the values of the probabilities for each primary treatment. These values are constant for the remaining living years of the patient, starting from the year that she goes through the surgery.

$$\begin{aligned} P(\textit{Change in appearance at Time} = t|\textit{No treatment}) &= 0 \\ P(\textit{Change in appearance at Time} = t|\textit{Mastectomy}) &= 1 \\ P(\textit{Change in appearance at Time} = t|\textit{Quadrantectomy}) &= 0.25 \\ P(\textit{Change in appearance at Time} = t|\textit{Lumpectomy}) &= 0.125 \end{aligned} \tag{9}$$

Cancer free: It is assumed that a healthy patient will not suffer any significant change in appearance for the rest of her life, so this probability is 0 for the rest of the years.

In situ: We assume the value of $P(\textit{Change in appearance at Time} = t)$ is of 1 for the rest of the life when a mastectomy is done. Given that a lumpectomy is done when the cancer state is not advanced, the change in appearance of this treatment is considered as half of that produced from quadrantectomy. Meaning that the wanted probability is of $0.25/2 = 0.125$ for the remaining living years of the patient.

Invasive: As mentioned earlier, if a mastectomy is done, the probability is 1 for the remaining living years of the patient. The probability is 0.25 if a breast conserving surgery is done. This is because the conservative surgery that is done for invasive cancer is quadrantectomy, where one-quarter of the breast is removed (ACS, 2014).

- Fatigue

  Lerdal et al. (2005) explored the relationship between fatigue and demographic variables including age using the Fatigue Severity Scale (FSS). The FSS is a scale that ranges from 1 to 9, where 9 represents the maximum fatigue. Their study suggests that a FSS value of 5 or greater should be defined as severe fatigue. Also, they reported the mean and standard deviation of the FSS scores for women in various groups of age. We assumed that the scores of each age group a'_t studied by Lerdal et al. (2005) follow a normal distribution $N(a'_t)$ which parameters $\mu(a'_t)$ and $\sigma(a'_t)$ are reported in their work. This then enabled us to compute the probability that a woman of age t has severe fatigue, that is $P(N(a'_t) > 5)$. This value is the same for each reported age group a'_t. Let $Fa(t)$ denote the probability that a woman without breast cancer has severe fatigue at time t. It was assumed that most of the people from Lerdal et al. (2005) did not develop breast cancer and were treated by the time of the survey, so the probability that we obtained is considered as the probability of having fatigue given that the decision is not to treat (Equation 10).

$$P(\textit{Fatigue at Time } = t|\textit{No treatment}) = Fa(t) = P(N(a'_t) > 5) \tag{10}$$

Cancer free: Given that the only decision of a cancer free patient is not to treat, the value of $P(\textit{Fatigue at Time} = t)$ corresponds to the natural progression of fatigue $Fa(t)$ as shown in Equation 10.

In situ and Invasive: Assuming that fatigue is a side effect produced by treatment, it does not depend on the cancer stage of the patient. If a treatment is done, the probability of having fatigue at a certain age should be increased by a factor. The methodology used to find that factor is based on the work of Bower et al. (2006), who evaluated the effects of treatment on the fatigue of breast cancer survivors. They found the proportion of cancer patients that were treated by a specific treatment given if they showed fatigue $(P(T|F))$ or not $(P(T|F^c))$. Here F refers to a fatigued patient and T is a treatment that could be surgery alone, surgery plus radiotherapy, surgery plus chemotherapy, surgery plus radiotherapy and chemotherapy and the use of current and in the past of tamoxifen. Using the Bayes formula and the proportion of patients that manifested being fatigued $P(F)$, it can be found that the probability that a patient is fatigued given that she is treated by a certain treatment, i.e., $P(F|T)$. In Bower et al. (2006) study, both fatigued and non fatigued patients have a mean age of approximately 59 years. We consider that the treatments have a stationary proportion of increment on fatigue as a function of age, meaning that a patient that was treated with a treatment type T has an increment on fatigue of $\dfrac{P(F|T) - F(59)}{F(59)}$ for the rest of her remaining years. The final result is shown in Equation 11.

$$P(\textit{Fatigue at Time} = t|T) = Fa(t) \times \frac{P(F|T) - F(59)}{F(59)} \tag{11}$$

- General Pain

  We consider general pain as the side effects produced immediately by the treatment, such as nausea, constipation and sleep problems. We assume that patients will always have this side effect when chemotherapy or hormone therapy is being used, i.e., $P(\textit{General Pain at Time} = t|\textit{Hormone therapy}) = 1$ for the time that the patient is being treated with hormone therapy. According to Clarke et al. (2005), the recommended time that a patient should take hormone therapy is 5 years. Senkus et al. (2013) suggest that chemotherapy usually lasts from 12 to 24 weeks. This leads to an average of 18 weeks of chemotherapy treatment from a year that has around 52 weeks. In that order of ideas we established that $P(\textit{General Pain at Time} = t|\textit{Hormone therapy}) = 18/52$ for the year that the patient is receiving the treatment.

$(Side\ Effect\ iEW)$ The value of $(Side\ Effect\ iEW)$ is determined by the patient answering the following question "What percentage of my remaining life would I willing to give up to avoid this side effect?". For example, if the answer of this question referring the side effect of being sterile is 30%, then the patient would consider 10 years being sterile equally as 7 years without this side effect.

3.3. Optimality Equations

We denote by $V_t(o)$ the maximum total expected life scores the patient can attain when the current observed cancer state is o at decision epoch t. Then,

$$V_t(o) = \begin{cases} \sum_{u \in S} q_u^t \left(r_t(u,1) + \lambda \sum_{s' \in \Omega} p_{us'}(a_t) V_{t+1}(s') \right) & o_t = 1 \\ \max \begin{cases} r_t(o,1) + \lambda \sum_{s' \in \Omega} p_{os'}(a_t) V_{t+1}(s') \\ r_t(o,a)\,,\ a \in A(o) \backslash \{1\} \end{cases} & o_t = 2,3 \end{cases}$$

For the case when the observation is cancer-free, we use the post-diagnosis cancer distribution to calculate the immediate and discounted future life scores that a patient may obtain. On the other hand, if in situ or invasive cancer is observed, the model will decide either to wait or treat depending on the maximum between the immediate plus the discounted future life scores and the estimation of expected life score for the remaining life corresponding to each treatment option. The terminal values at year 100 for the decision making process are defined below:

$$V_{100}(o) = \begin{cases} \sum_{u \in S} q_u^{100} \left(r_{100}(u,1) \right) & o_t = 1 \\ \max \begin{cases} r_{100}(o,1) \\ r_{100}(o,a)\,,\ a \in A(o) \end{cases} & o_t = 2,3 \end{cases}$$

4. SOURCES OF MODEL INPUTS AND ESTIMATIONS

In this section we present the methodology how each of the parameter of the model is obtained.

4.1. Post-diagnosis cancer distribution

We are going to use the values of q_1^t, q_2^t and q_3^t that Vargas et al. (2014) obtained for each age group.

4.2. Transition Probability Matrices

We estimate the 1-year transition probabilities of natural progression of breast cancer. We took as reference the methodology proposed by Maillart et al. (2008), who used 6-month transition probabilities, in order to build those matrices. Table 3 summarizes the sources of the elements of the transition probabilities.

- $p_{12}(a_t)$: It is the probability of advancing form a cancer free state to an in situ state. It was computed with Maillart et al. (2008) 6-month transition probabilities $p_{ij}^M(a_t)$, as in Equation 12. The first part of the equation refers to the probability of advancing in the first 6 months to an in situ stage and in the next six months the patient stays in that

Table 3: Sources of the transition probabilities

Item	Source
$p_{12}(a_t)$	Maillart et al. (2008)
$p_{14}(a_t)$ & $p_{24}(a_t)$	CDC et al. (2011)
	SEER (2010)
$p_{23}(a_t)$	Tabar et al. (2000)
$p_{33}(a_t)$	Bloom et al. (1962)

stage. The second term of the equation is the probability of staying in the first semester in the cancer free state and then advance to the in situ stage in the second semester.

$$p_{12}(a_t) = p^M_{12}(a_t) \cdot p^M_{22}(a_t) + p^M_{11}(a_t) \cdot p^M_{12}(a_t) \tag{12}$$

- $p_{14}(a_t)$ & $p_{24}(a_t)$: They are the probabilities of dying from causes other than breast cancer. Equation 13 shows how this probability was estimated. CDC (2011) reported the result of death rates in 2009 in the U.S. for all types of causes including breast cancer. Because breast cancer death can only be achieved from the invasive state, we subtract the death from breast cancer rate obtained from SEER (2010).

$$p_{14}(a_t) = p_{24}(a_t) = \textit{CDC mortality rate}(a_t) - \textit{SEER BC mortality rate}(a_t) \tag{13}$$

- $p_{23}(a_t)$: This is the one-year probability of advancing from an in situ stage to an invasive stage. We use Tabar et al. (2000) mean sojourn time to find the probability as in Equation 14.

$$p_{23}(a_t) = \frac{1}{\textit{Tabar Mean Sojourn Time}(a_t)} \tag{14}$$

- $p_{33}(a_t)$: This is the probability that a patient in an invasive stage survives for one year without treatment. Bloom et al. (1962) estimated the survival of breast cancer patients without treatment and found a proportion of patients who survived for at least three years. Equation 15 shows an equality that can be used to compute $P_{33}(a_t)$.

$$\textit{Bloom's three year untreated survival}(a_t) = p_{33}(a_t)^3 \tag{15}$$

- $p_{11}(a_t)$, $p_{22}(a_t)$ & $p_{34}(a_t)$: These probabilities are computed as the complement of the rest of the probabilities of each row.

$$\begin{aligned} p_{11}(a_t) &= 1 - p_{12}(a_t) - p_{14}(a_t) \\ p_{22}(a_t) &= 1 - p_{23}(a_t) - p_{24}(a_t) \\ p_{34}(a_t) &= 1 - p_{33}(a_t) \end{aligned}$$

5. RESULTS

In this section, we introduce the numerical experiments that we performed with example patient's specific parameters. Then we discuss and analyse the results obtained.

5.1. Numerical Experiments

Life Scores In this section we present the values of the life scores for each type of treatment for an example patient. The values of the emotional weights *Side Effect i EW* of this patient are 15%, 5%, 5% and 2% for the side effects of recurrence, change in appearance, fatigue and general pain, respectively. We refer to this patient as *example patient 1*. Assuming the patient is at age 40, diagnosed with in situ cancer and estrogen receptor positive, then Figure 3 shows the different life scores for each type oftreatment. It can be concluded that the decision number 4, which suggest doing a breast conserving surgery followed by radiotherapy, is the best option for this example patient.

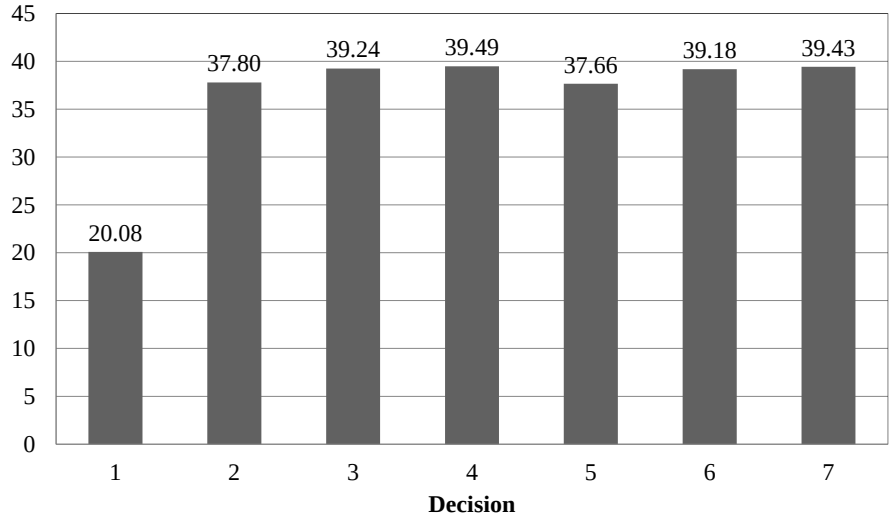

Figure 3. Life scores for each treatment decision of the example patient 1, who is 40 years, in situ breast cancer and estrogen receptor positive.

Also, we present the results of the life scores at different ages and cancer stages using the emotional weights for the example patient 1. Figures 4 and 5 show how the values decrease with age for both in situ and invasive cases, respectively. Note that in general, the life score decreases with age and the differences between the decisions also decreases. This suggests that for older patients, the treatment decision gain is almost the same for all possible actions. This could be explained by taking into account that the life expectancy of the older patients is less than that of the younger patients, implying that they might live less years with the side effects than the younger patients. So in order to avoid those side effects and because life expectancy is almost the same if the decision is to treat, some elderly patients would prefer not to treat instead of treating.

In order to see how the best treatment changes with the emotional weights of a patient, we made a sensitivity analysis showed in Table 4. In this case, the patient is 40 years old, is in an invasive stage and is ER+. We varied two of the four emotional weights from 0 to 1, in steps of 0.2. The remaining emotional weights are set in 0.2. The treatment whose life score is the greatest is showed.

Markov Decision Process In order to solve the model, we established the values of the emotional weights *Side Effect i EW* of the patient as the proposed by the example patient 1 (15%, 5%, 5% and 2% for the side effects of recurrence, change in appearance, fatigue and general pain respectively). The weights depend on the patient's personal preferences, so the final result of the implementation can change between patients. In addition, the patient is assumed to be ER positive, meaning that treatments with hormone therapy are also an option for her. We solve our MDP model to optimality using the *Backward Induction* algorithm (Puterman, 1994). Five different scenarios were defined in order to assess the optimal treatment policy if the patient is diagnosed with in situ or invasive cancer at a given age. In the first scenario we evaluate the performance of

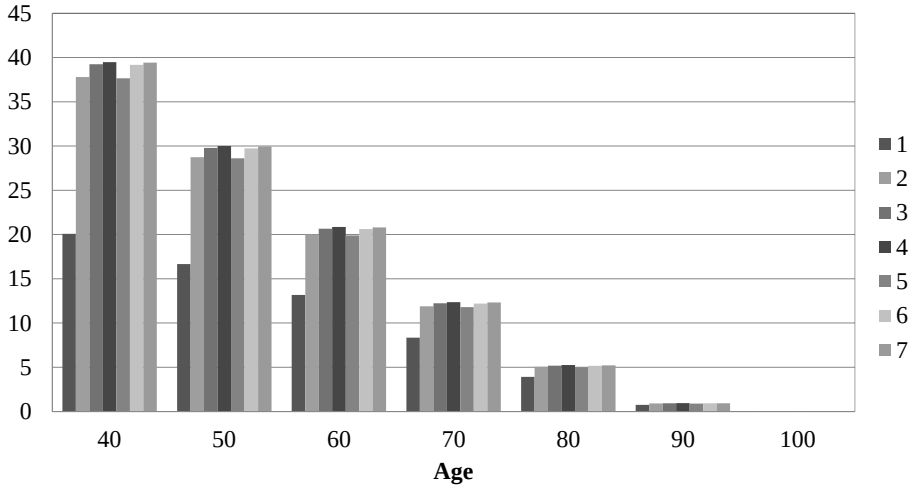

Figure 4. Life scores for each possible decision by age for the example patient 1 in an in situ cancer stage and estrogen receptor positive.

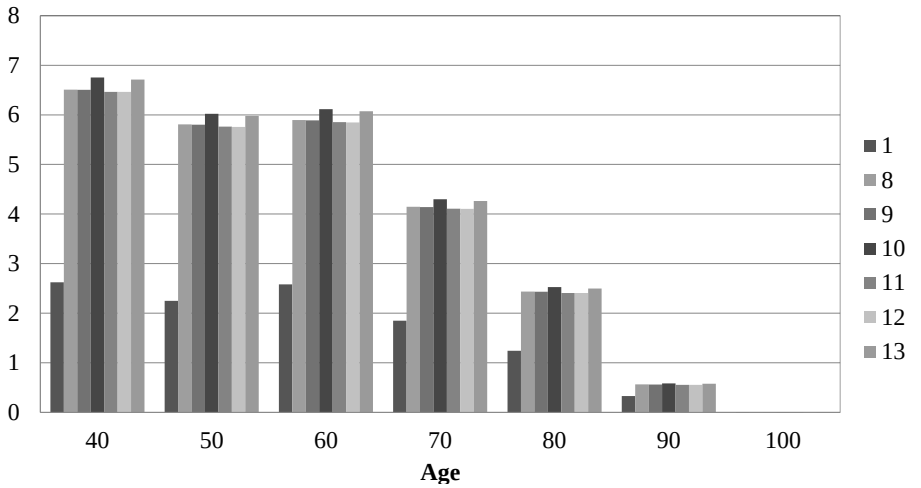

Figure 5. Life scores for each possible decision by age for the example patient 1 in an invasive cancer stage and estrogen receptor positive.

our model when none of the considerations regarding cancer regression and type II error in mammography results are taken into account. Scenarios 2 to 4 include the modifications proposed by Zhang and Ivy (2012b) related to cancer regression, all of them with an average regression rate of 20%, but does not consider type II error in mammography results; in the second scenario $u = v$, in the third $u < v$ and in the fourth $u > v$. Finally, the fifth scenario presents the optimal policy including all considerations regarding cancer regression and type II error; this scenario considers the same u and v values as in the second scenario to incorporate cancer regression. Table 5 presents the results obtained for each scenario.

To test the effect of the patient's personal preference in the model we considered a second example patient. The emotional weights *Side Effect i EW* for this patient are 90%, 5%, 5% and 2% for the side effects of recurrence, change in appearance, fatigue and general pain (*example patient 2*). Note that the only difference between this patient and the patient 1 is that the recurrence weight is now 90% instead of 15%. Table 6 shows the optimal treatment policy for the patient 2 for the five scenarios described before. We assume this patient has estrogen receptor positive breast cancer.

Table 4: Best treatment decision varying two of the four emotional weights of a 40 year old ER+ invasive patient. The other two emotional weight parameters are set in 0.2.

Appearance EW \ Recurrence EW	**0**	**0.2**	**0.4**	**0.6**	**0.8**	**1**
0	8	8	8	8	9	9
0.2	10	10	10	10	10	10
0.4	10	10	10	10	10	10
0.6	10	10	10	10	10	10
0.8	10	10	10	10	10	10
1	10	10	10	10	10	10

Fatigue EW \ Appearance EW	**0**	**0.2**	**0.4**	**0.6**	**0.8**	**1**
0	9	10	10	10	10	10
0.2	8	10	10	10	10	10
0.4	8	10	10	10	10	10
0.6	8	10	10	10	10	10
0.8	8	10	10	10	10	10
1	8	10	10	10	10	10

Fatigue EW \ Recurrence EW	**0**	**0.2**	**0.4**	**0.6**	**0.8**	**1**
0	10	10	10	10	10	10
0.2	10	10	10	10	10	10
0.4	10	10	10	10	10	10
0.6	10	10	10	10	10	10
0.8	10	10	10	10	10	10
1	10	10	10	10	10	10

G. Pain EW \ Appearance EW	**0**	**0.2**	**0.4**	**0.6**	**0.8**	**1**
0	8	13	13	13	13	13
0.2	8	10	10	10	10	10
0.4	8	10	10	10	10	10
0.6	8	10	10	10	10	10
0.8	8	10	10	10	10	10
1	8	10	10	10	10	10

G. Pain EW \ Recurrence EW	**0**	**0.2**	**0.4**	**0.6**	**0.8**	**1**
0	10	13	13	13	13	13
0.2	10	10	10	10	10	10
0.4	10	10	10	10	10	10
0.6	10	10	10	10	10	10
0.8	10	10	10	10	10	10
1	10	10	10	10	10	10

G. Pain EW \ Fatigue EW	**0**	**0.2**	**0.4**	**0.6**	**0.8**	**1**
0	13	13	13	13	13	13
0.2	10	10	10	10	10	10
0.4	10	10	10	10	10	10
0.6	10	10	10	10	10	10
0.8	10	10	10	10	10	10
1	10	10	10	10	10	10

5.2. Discussion

Life Score Life score is a metric that seeks to take into account the patient's expected remaining life years and her personal preferences given a specific treatment or no treatment decision. This metric implies that no other decision will be done for the rest of the patient's remaining life. As a consequence, the life score associated to no treatment decision for invasive or in situ patients are usually lesser than the other treatments. What life scores do not consider is to do a possible future treatment decision after choosing doing no treatment. The Markov decision process takes this issue into account, suggesting no treatment decisions for elderly patients.

Life score also considers the difference between different cancer stages. As showed in Figures 4 and 5, the average life score of the invasive cancer patients is around one quarter of the average life score of in situ patients. This difference is caused because of the higher probability of dying from breast cancer for advanced cancer patients (a decrease in the 5-year no treatment cause specific survival probability of a 40-year patient from 88.0% for the in situ state to 27.4% for the invasive state).

Also, because life scores consider the patient's personal preferences, the best treatment decision changes between patients. According to Table 4 the decision number 10, that consists of doing a breast conserving surgery plus radiotherapy and chemotherapy, is the most common when the emotional weights are high (greater than 0.2). It can be inferred that this treatment is the one that have less effects on the side effects, i.e. breast conserving surgery have less effect than mastectomy in the appearance, but have a higher probability of developing recurrence. To avoid that, the adjuvant treatments of radiotherapy

Table 5: Optimal treatment policy for in situ and invasive breast cancers for the example patient 1 considering three different scenarios

Scenario	**1**		**2**		**3**		**4**		**5**			**1**		**2**		**3**		**4**		**5**	
Age	**IS**	**INV**	**IS**	**INV**	**IS**	**INV**	**IS**	**INV**	**IS**	**INV**	**Age**	**IS**	**INV**	**IS**	**INV**	**IS**	**INV**	**IS**	**INV**	**IS**	**INV**
40	4	10	4	10	4	10	4	10	4	10	71	4	10	4	10	4	10	4	10	4	10
41	4	10	4	10	4	10	4	10	4	10	72	4	10	4	10	4	10	4	10	4	10
42	4	10	4	10	4	10	4	10	4	10	73	4	10	4	10	4	10	4	10	4	10
43	4	10	4	10	4	10	4	10	4	10	74	4	10	4	10	4	10	4	10	4	10
44	4	10	4	10	4	10	4	10	4	10	75	4	10	4	10	4	10	4	10	4	10
45	4	10	4	10	4	10	4	10	4	10	76	4	10	4	10	4	10	4	10	4	10
46	4	10	4	10	4	10	4	10	4	10	77	4	10	4	10	1	10	4	10	4	10
47	4	10	4	10	4	10	4	10	4	10	78	4	10	1	10	1	10	1	10	4	10
48	4	10	4	10	4	10	4	10	4	10	79	4	10	1	10	1	10	1	10	4	10
49	4	10	4	10	4	10	4	10	4	10	80	4	10	1	10	1	10	1	10	4	10
50	4	10	4	10	4	10	4	10	4	10	81	4	10	1	10	1	10	1	10	4	10
51	4	10	4	10	4	10	4	10	4	10	82	4	1	1	1	1	1	1	1	1	10
52	4	10	4	10	4	10	4	10	4	10	83	1	1	1	1	1	1	1	1	1	1
53	4	10	4	10	4	10	4	10	4	10	84	1	1	1	1	1	1	1	1	1	1
54	4	10	4	10	4	10	4	10	4	10	85	1	1	1	1	1	1	1	1	1	1
55	4	10	4	10	4	10	4	10	4	10	86	1	1	1	1	1	1	1	1	1	1
56	4	10	4	10	4	10	4	10	4	10	87	1	1	1	1	1	1	1	1	1	1
57	4	10	4	10	4	10	4	10	4	10	88	1	1	1	1	1	1	1	1	1	1
58	4	10	4	10	4	10	4	10	4	10	89	1	1	1	1	1	1	1	1	1	1
59	4	10	4	10	4	10	4	10	4	10	90	1	1	1	1	1	1	1	1	1	1
60	4	10	4	10	4	10	4	10	4	10	91	1	1	1	1	1	1	1	1	1	1
61	4	10	4	10	4	10	4	10	4	10	92	1	1	1	1	1	1	1	1	1	1
62	4	10	4	10	4	10	4	10	4	10	93	1	1	1	1	1	1	1	1	1	1
63	4	10	4	10	4	10	4	10	4	10	94	1	1	1	1	1	1	1	1	1	1
64	4	10	4	10	4	10	4	10	4	10	95	1	1	1	1	1	1	1	1	1	1
65	4	10	4	10	4	10	4	10	4	10	96	1	1	1	1	1	1	1	1	1	1
66	4	10	4	10	4	10	4	10	4	10	97	1	1	1	1	1	1	1	1	1	1
67	4	10	4	10	4	10	4	10	4	10	98	1	1	1	1	1	1	1	1	1	1
68	4	10	4	10	4	10	4	10	4	10	99	1	1	1	1	1	1	1	1	1	1
69	4	10	4	10	4	10	4	10	4	10	100	1	1	1	1	1	1	1	1	1	1
70	4	10	4	10	4	10	4	10	4	10											

IS: In situ state, INV: Invasive state, Scenario 1: no regression and no type II error, Scenario 2: regression ($u = 0.21$, $v = 0.21$) and no type II error, Scenario 3: regression ($u = 0.15$, $v = 0.35$) and no type II error, Scenario 4: regression ($u = 0.23$, $v = 0.15$) and no type II error, Scenario 5: regression ($u = 0.21$, $v = 0.21$) and type II error.

and chemotherapy are implemented. This does not mean that the best treatment is always this combination of treatments because patients may not assign high values to the emotional weights parameters.

Cancer Regression and Type II error Cancer regression is also an important issue. According to the model results of the first patient, considering regression will help avoid overtreatment for 4 years of treatment for the in situ case. In the case that the patient has an invasive cancer, cancer regression does not affect the optimal policy because our model considers regression only from the in situ stage. On the other hand if type II error is also considered, more treatment decisions have to be done in order to avoid the potential delay in cancer detection. Our final model is described by the third scenario, where both type II error and regression are considered.

Markov Decision Process It can be seen that although all alternatives of treatments were implemented in the model, for the patient 1 only three of them are the best for her depending on the cancer stage and age: conducting a breast conserving surgery followed by a radiotherapy for both stages and add chemotherapy if the stage of the cancer is invasive. Hormone therapy is not considered in any case, implying that the optimal treatment is not always giving the patient hormone therapy when the patient is ER positive. In addition, considering no treatment option for both in situ and invasive stages is essential

Table 6: Optimal treatment policy for in situ and invasive breast cancers for the example patient 2 considering three different scenarios

Scenario	**1**		**2**		**3**		**4**		**5**			**1**		**2**		**3**		**4**		**5**	
Age	**IS**	**INV**	**IS**	**INV**	**IS**	**INV**	**IS**	**INV**	**IS**	**INV**	**Age**	**IS**	**INV**	**IS**	**INV**	**IS**	**INV**	**IS**	**INV**	**IS**	**INV**
40	7	13	7	13	7	13	7	13	7	13	71	7	13	7	13	7	13	7	13	7	13
41	7	13	7	13	7	13	7	13	7	13	72	7	13	7	13	7	13	7	13	7	13
42	7	13	7	13	7	13	7	13	7	13	73	7	13	7	13	7	13	7	13	7	13
43	7	13	7	13	7	13	7	13	7	13	74	7	13	7	13	7	13	7	13	7	13
44	7	13	7	13	7	13	7	13	7	13	75	7	13	7	13	7	13	7	13	7	13
45	7	13	7	13	7	13	7	13	7	13	76	7	13	7	13	7	13	7	13	7	13
46	7	13	7	13	7	13	7	13	7	13	77	7	13	7	13	7	13	7	13	7	13
47	7	13	7	13	7	13	7	13	7	13	78	2	13	2	13	2	13	2	13	2	13
48	7	13	7	13	7	13	7	13	7	13	79	2	13	2	13	2	13	2	13	2	13
49	7	13	7	13	7	13	7	13	7	13	80	2	13	2	13	2	13	2	13	2	13
50	7	13	7	13	7	13	7	13	7	13	81	2	13	2	13	2	13	2	13	2	13
51	7	13	7	13	7	13	7	13	7	13	82	2	10	1	10	1	10	1	10	2	10
52	7	13	7	13	7	13	7	13	7	13	83	2	10	1	10	1	10	1	10	2	10
53	7	13	7	13	7	13	7	13	7	13	84	2	10	1	10	1	10	1	10	2	10
54	7	13	7	13	7	13	7	13	7	13	85	2	10	1	10	1	10	1	10	2	10
55	7	13	7	13	7	13	7	13	7	13	86	2	10	1	10	1	10	1	10	2	10
56	7	13	7	13	7	13	7	13	7	13	87	2	10	1	10	1	10	1	10	1	10
57	7	13	7	13	7	13	7	13	7	13	88	2	10	1	10	1	10	1	10	1	10
58	7	13	7	13	7	13	7	13	7	13	89	2	10	1	10	1	10	1	10	1	10
59	7	13	7	13	7	13	7	13	7	13	90	4	10	1	10	1	10	1	10	1	10
60	7	13	7	13	7	13	7	13	7	13	91	4	10	1	10	1	10	1	10	1	10
61	7	13	7	13	7	13	7	13	7	13	92	4	10	1	10	1	10	1	10	1	10
62	7	13	7	13	7	13	7	13	7	13	93	4	10	1	10	1	10	1	10	1	10
63	7	13	7	13	7	13	7	13	7	13	94	1	1	1	1	1	1	1	1	1	10
64	7	13	7	13	7	13	7	13	7	13	95	1	1	1	1	1	1	1	1	1	1
65	7	13	7	13	7	13	7	13	7	13	96	1	1	1	1	1	1	1	1	1	1
66	7	13	7	13	7	13	7	13	7	13	97	1	1	1	1	1	1	1	1	1	1
67	7	13	7	13	7	13	7	13	7	13	98	1	1	1	1	1	1	1	1	1	1
68	7	13	7	13	7	13	7	13	7	13	99	1	1	1	1	1	1	1	1	1	1
69	7	13	7	13	7	13	7	13	7	13	100	1	1	1	1	1	1	1	1	1	1
70	7	13	7	13	7	13	7	13	7	13											

IS: In situ state, INV: Invasive state, Scenario 1: no regression and no type II error, Scenario 2: regression ($u = 0.21$, $v = 0.21$) and no type II error, Scenario 3: regression ($u = 0.15$, $v = 0.35$) and no type II error, Scenario 4: regression ($u = 0.23$, $v = 0.15$) and no type II error, Scenario 5: regression ($u = 0.21$, $v = 0.21$) and type II error.

on the decision process. The side effects of treatments can affect more the older patients. This may be caused by the fact that older patients have less remaining life years than younger patients, so these patients would prefer to live those remaining years without the possible side effects of treatment.

From Table 6, it can be concluded that a patient's personal preference affect the optimal policy. In the second case, the patient would prefer to sacrifice 90% of her remaining life in order to avoid having a recurrent cancer. The treatments for this patient should be the ones that reduce the probability of having a recurrent cancer after a treatment. That is the reason why hormone therapy, which helps to reduce cancer recurrence, is included in most of the treatments. In the case that the patient is in an invasive stage, all adjuvant treatments have to be implemented until the age of 81 years (scenario 1). Then, for the next 11 years the patient should stop taking hormone therapy, probably because this adjuvant treatment do not reduce significantly the recurrence and affect both fatigue and general pain of the patient.

Comparing Tables 5 and 6, it is evident the preference to avoid recurrence in the threshold of not doing any treatment. While the example patient 1 has a threshold of no treatment at the age of 83 (in situ) or 82 (invasive) years for the first scenario, the second patient has the same threshold at the age of 94 years. In this case, the patient will prefer to treat at an advanced age in order not to have any type of recurrent cancer, although it implies having the other side effects of treatment.

It is important to remember that although the model obtains the best treatment policy for a patient, other factors need to be taken into account when selecting the final decision. Despite the model tries to maximize the quantity and quality of life of the patient, it considers that all of the treatments are always available. Some factors like the demographical and economic affect the availability of the treatments. Berkowitz et al. (2000) found that on average the yearly costs of hospitalization and professional fees per patient are of $10,087. The yearly cost of radiotherapy, hormone therapy and chemotherapy per patient are of $1,590, $168 and $466 respectively (1998 US dollars). This may cause that a patient that have limited economical resources would choose a treatment different than the one that the model suggests, sacrificing some quality of life caused by the limitation of her economic situation. Also, it is possible that one of the treatment decisions is not available in the location of the patient. This would imply that some additional cost of transportation have to be paid, increasing the total cost of the treatment.

6. CONCLUSIONS

A Markov decision process model has been proposed in this work. It finds the optimal treatment policy for breast cancer patients considering various parameters such as cancer stage, hormonal receptor status and the patient's personal preference over the different side effects. In order to build the model, the immediate rewards were proposed to be life scores, a metric that measure both the quantity and quality of the remaining life years of the patient. The advantage of using this metric instead of the most used metric in medical projects, QALY, is that the life score considers the patient's emotional opinion about the different side effects. As discussed in section 5, the life scores vary according to the age, treatment and patient's preferences, making this metric a good proposal for the immediate rewards of the Markov decision process.

Moreover, it was shown that the optimal treatment policy varies with the patient's personal preferences. That suggests that not only the physician makes the treatment decision, but the woman should be also included in the decision process. Another interesting fact found by the optimal policy is that making a treatment for elderly patients is not always recommended because the gain in life years is not very significant and treatment implies having side effects for the few remaining life of the patient. Despite of this, the threshold of no treatment decisions depends on the patient as discussed in Section 5.2.

Finally, considering cancer regression from an in situ stage and type II error on mammography results affect the optimal treatment policy. In order to build a model that approximates the reality better, both medical facts should be considered in the model. The proposed model gives an optimal treatment policy for breast cancer patients. The next step on this project is to evaluate the performance of model with real cases of study and make the possible modifications to make it more accurate. In that way, the model can be implemented as an important part of breast cancer treatment procedures. It is also important to note that the model approximate the complexity of the decision process and only gives a suggestion of the best treatment for a patient. The final treatment decision should be done by both the physician and the patient, and consider the results of the model as a guide to take that decision.

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