Scheduling the Adjuvant Endocrine Therapy for Early Stage Breast Cancer

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Based on the data available through published trial results, we build a mixed integer nonlinear programming (MINLP) model in order to find an optimal treatment plan for a given Hr+ early stage breast cancer patient who is postmenopausal. The objective is to maximize the weighted sum of (1) disease free survival percentage at the end of the treatment period; (2) the negative of the risk of contralateral breast cancer; (3) the slack variables used in the constraints for the risks of several side effects, including endometrial cancer, thromboembolic events, cardiovascular diseases, bone fractures, hot flushes, and vaginal bleeding. The results of numerical experiments suggest the effectiveness of some of the schedules currently used in practice, as well as indicate some effective alternative treatment plans.

Key words: Breast cancer, adjuvant endocrine therapy, scheduling, mathematical programming

1. Introduction

Breast cancer is the most commonly diagnosed cancer among women in the United States and worldwide (excluding skin cancer), accounting for nearly 1 in 3 cancers in US women. The National Cancer Institute estimates that a woman in the United States has a 1 in 8 chance of developing invasive breast cancer during her lifetime. Furthermore it is the leading cause of cancer death among women worldwide. Approximately 40,460 women in the U.S. will die from the disease in 2007. American Cancer Society (2006). Previous studies had shown cancer death rates in the US decreasing by an average of 1.1% a year from 1993 through 2002. The latest report shows evidence that the decline in cancer deaths nearly doubled from 2002 through 2004, with an average decrease of 2.1% seen each year. This decline is credited to the effectiveness of prevention efforts, new screening methods and wider use of early detection, and better treatments that have extended life expectancy after diagnosis. American Cancer Society (2006). Research on these fields will yield further improvements.

The cancer treatments can be classified as local or systemic. The purpose of local treatment is to treat a tumor without affecting the rest of the body. Surgery and radiation are examples of local treatment. Systemic treatment is given into the bloodstream or by mouth to go throughout the body and reach cancer cells that may have spread beyond the breast. Chemotherapy, endocrine therapy, and immunotherapy are systemic treatments. The systemic treatment given to a patient before surgery to shrink the tumor is called neoadjuvant therapy. It is called adjuvant if it is given after surgery in order to kill cancer cells that might have broken away from the main tumor and begun to spread through the bloodstream in the early stages of the disease. American Cancer Society (2006).

Research conducted in 1960s has shown that some forms of breast cancer are dependent on hormones for growth. Such tumors contain hormone receptors and are called Hr+(hormone receptor-positive). About two-thirds of women with breast cancer have tumors that contain estrogen receptors. To prevent the fast growth of such cancer cells, there are two alternative ways: one is to

decrease the level of estrogen; and the other is to block the estrogen receptors from binding with estrogen. A drug called Tamoxifen, which was introduced to clinical settings in early 1970s, slows down the growth of cancer cells by preventing estrogen from binding to its receptor Buzdar (2005). Since then, Tamoxifen has proved to be very effective on many breast cancer patients. For this reason, Tamoxifen has been the primary adjuvant endocrine treatment for postmenopausal women with HR+ breast cancer for years.

Although Tamoxifen has preventive effects on cardiovascular diseases and bone loss, it is associated with some side effects, which can be as serious as endometrial cancer or thromboembolic events. In particular, Tamoxifen has been shown to double the risk of endometrial cancer after 1 or 2 years of treatment and quadruple the risk after 5 years of treatment Early Breast Cancer Trialist's Collaborative Group (1998). The relation between Tamoxifen and endometrial cancer is time independent and irrespective of dose, and the risk does not decrease after stopping the treatment Bergman et al. (2000), Duffy et al. (2006). Furthermore, many women develop resistance to the drug over time, leading to cancer recurrence. In addition, because Tamoxifen binds directly to the estrogen receptor, it can sometimes activate the signaling pathways it was designed to block. National Cancer Institute (2008).

The increasing complaints about the side effects of Tamoxifen encouraged the researchers to come up with new ideas. The Aromatase Inhibitors (AIs), which prevent the conversion of the androgens to estrogen, were first introduced in late 1970s. When a woman is post menopause, nearly all of the estrogen in her body is made outside the ovaries. This estrogen is made when a male-like hormone, androgen, from the adrenal glands (which sit atop the kidneys) is converted into estrogen by an enzyme called aromatase. By stopping aromatase activity, AIs decrease the amount of estrogen available. Instead of blocking the estrogen receptors, like Tamoxifen, AIs prevent the formation of estrogen Buzdar (2005). Since late 1970s, several AIs were developed. The first- and second-generation AIs; aminoglutethimide, formestane, and fadrozole; had no significant benefits over Tamoxifen. But the third-generation AIs; Anastrozole, Letrozole, Exemestane; seem promising according to the results of the clinical trials ATAC Trialist Group (2004), Thürliman (2005), Coombes et al. (2004), Goss et al. (2003), Jakesz and Menzel (2005).

Our motivation in this study is the lack of consensus on the endocrine therapy schedules. Although the results of some trials show that third-generation AIs can be more effective than Tamoxifen in terms of preventing recurrences, there is still no clear information about which schedule is the best for a given patient. Our aim is to design effective adjuvant endocrine therapy plans for postmenopausal women with Hr+, early stage breast cancer based on the data from clinical trials available in the literature. In this paper, we present a mixed integer nonlinear programming (MINLP) model, which utilizes the data from published trials in order to estimate the dependencies between the incidences of side effects and the duration of a therapy. The objective is to maximize the disease free survival chance while keeping some important side effects within tolerable limits for the patient.

The remainder of this paper is organized as follows. Section 2 presents a brief review of related literature. Section 3 describes the proposed MINLP model in detail. Section 4 discusses the results of numerical testing of the proposed approach, and Section 5 is devoted to some concluding remarks. Finally, Appendices A-C contain the description of cancer stages, trial settings, and brief summary of published trial results that were used to develop our model.

2. Literature Review

A typical cancer treatment consists of several therapy modalities such as surgery, radiotherapy, chemotherapy, endocrine therapy, as well as other, novel approaches. Operations research (OR) methods have been applied extensively to problems related to various aspects of cancer treatment, such as the detailed scheduling of radiotherapy and chemotherapy Beil and Wein (2001). For

example, a common optimization problem arising in radiotherapy is to determine the number, positioning and the intensity of radiation beams so that the maximum number of cancer cells in a tumor are eliminated, while constraining the dosage of radiation obtained by healthy tissues around the targeted tumor (see, e.g., Brahme (2001), Hamacher and Küfer (2002), Lee et al. (2003), Ferris et al. (2003), Romeijn et al. (2006)). Similarly, in chemotherapy one is interested in finding the optimal dose and frequency of a drug so that the tumor size is minimized while keeping the number of normal cells above a certain level and limiting toxicity. Starting in 70s, there has been extensive research done on the theoretical investigation of cancer chemotherapy control methods Shin and Pado (1982), Barbolosi and Iliadis (2001), Agur et al. (2006), Fister and Panetta (2000). Differential equations, models of cell kinetics and drug kinetics are widely used in this research area. A recent paper Agur et al. (2006) proposes to use heuristics such as simulated annealing to optimize chemotherapy scheduling. The objective is to eliminate the cancerous cells, while maintaining a sufficiently high level of healthy cells Agur et al. (2006). To asses the fitness or the quality of each solution, the authors of Agur et al. (2006) consider the patient's condition at a common predetermined time. The factors that are taken into account include the number of normal cells and cancerous cells at that predetermined time.

As mentioned above, a cancer treatment usually consists of several types of therapies, therefore, an important decision is to determine a right sequence of all the therapies involved. The paper Beil and Wein (2001) proposes an optimization model for determining a sequence in which surgery (S), chemotherapy (C) and radiotherapy(R) should be administered. The problem is modeled using a system of ordinary differential equations that captures various local and systemic effects of each of these therapies. The objective is to maximize the cancer cure probability subject to toxicity constraints. The authors of Beil and Wein (2001) analytically show that SRCR and RSCR are two best-performing schedules among the eight considered variants, which also included the six permutations of S, C and R.

While a considerable amount of work has been done applying OR in radiotherapy and chemotherapy scheduling, there is little work done with respect to the endocrine therapy scheduling. This could be partially explained by limited availability of information on the effects of newly introduced endocrine therapy agents, such as third-generation AIs. The only way to observe these effects is through clinical trials. Although several trials have already been conducted, some of the published results still have to pass the test of time to be used as a conclusive evidence. Several other trials are currently at the stage of recruiting patients. Appendices B and C contain a list of current trial settings and a brief summary of the published trial results that are used in the present study.

Based on the available trial data Punglia et al. (2005) developed Markov models to investigate the effectiveness of different adjuvant endocrine therapy schedules. The outcomes that they consider are disease-free survival(DFS), distant disease-free survival, average time spent without the disease and average time spent without distant disease. The distant disease refers to a new cancer in some other part of the body. These models simulate the transition between the following three health states: (1) well with no recurrence of cancer; (2) having recurrent local or regional disease; (3) being diagnosed with a new primary cancer and having metastatic disease. They analyze the following treatment strategies: (a) Tamoxifen alone for 5 years; (b) AI alone for 5 years; and (c) sequential therapy with Tamoxifen for 2.5 or 5 years followed by an AI for 5 years. They use a time horizon of 10 years and recommend sequential adjuvant therapy with Tamoxifen followed by an AI after 2.5 years based on their model.

The authors of Cuzick et al. (2006) build mathematical models to explore the long-term (10 year) impact of different hormone treatment strategies reported in the clinical trials. As the measure of efficacy, they use percent of time lost to recurrence, which is obtained by integrating the recurrence curves. They propose two types of models. The *surface model* uses the available trial data in the most straightforward way to predict outcomes. The *deep model* aims to explain the data by an

underlying mechanistic model. The deep model assumes that there is a pressure toward phenotypic shift of micro metastases from $PgR+$ (progesterone-receptor +) to $PgR-$ (progesterone-receptor -) during the Tamoxifen treatment. If this assumption is true, a better efficiency obtained by sequencing AIs after Tamoxifen would not suggest that it is better to start with Tamoxifen, but would instead reflect a shift towards progesterone-receptor negativity and a more rapid development of resistance with it. The authors use a Markov model to represent this shift. The surface model recommends to use a mono therapy with an AI. The deep model, depending on its parameters, also favors sequencing an AI after Tamoxifen.

While the Markovian assumption allows to utilize the well-developed methodology of Markov processes, it is not clear how practical such assumption is. In fact, it appears to be more reasonable to think that the history of up-to-date treatments has a considerable impact on how the future treatments will affect a patient. Moreover, the previously proposed models have a very limited number of possible states, which do not take into account many important side effects. Therefore, a stochastic programming approach Birge and Louveaux (1997) appears to be more realistic. However, in order to take advantage of the stochastic programming methodology, one needs to have a large amount of trial data collected for different scenarios describing a patient's conditions at different stages of a treatment. Such data are necessary for the purpose of obtaining realistic estimates of the corresponding probabilities. Unfortunately, the currently available data sets do not provide the required amount of detail, and using poor quality estimates of probabilities may lead to erroneous conclusions. On the other hand, collecting the data containing all particular information is a time-consuming matter, which is also complicated by the constant increase in the number of available drugs. In view of the above discussion, we propose to use a deterministic mathematical programming approach, which attempts to utilize the clinical trial data in the form they are available in the literature. Namely, based on the data available through published trial results, we build a mixed integer nonlinear programming (MINLP) model in order to find an optimal treatment plan for a given Hr+ early stage (stages 0, 1, 2A, and 2B in Table 8 of Appendix A) breast cancer patient who is postmenopausal.

During the actual course of the treatment, the doctor can make changes on the proposed plan due to reasons such as the unexpected adverse conditions or some newly introduced more promising drugs. Although it is not dynamic, we believe that our model serves as a valuable tool to make the decision upfront using the available information. This is due to the fact that the first years of the treatment are more important than the rest because of the increased likelihood of recurrence.

3. A Mathematical Programming Model

Before we introduce the model, some general remarks concerning the clinical trial data used are in order. As discussed above, the available data sets do not provide any information that would allow to distinguish between different groups of patients, therefore we assume that we are dealing with an "average" postmenopausal Hr+ early stage breast cancer patient. It is also important to note that the clinical trials used to collect the data were carried out independently of each other, and hence some of the results have been recorded in a different fashion. For instance, the events included in the definition of disease free survival are different in some trials in terms of including or excluding death without a prior cancer event. More specific assumptions will be explained as we introduce the decision variables and the equations of the model.

We consider two sets of therapies to determine a treatment plan. These sets are defined as:

Set I : First step therapies, which are Tamoxifen (t_1), Anastrozole (a_1) and Letrozole (l_1).

Set J : Second step therapies, which are Anastrozole (a_2), Exemestane (e_2) and Letrozole (l_2).

The reason for this classification is that using AIs after Tamoxifen may have different effects on a patient compared to the situation when these drugs are used in the reverse order. Hence we

assume that the effectiveness of a therapeutic agent depends on the former agents. In the above classification, we did not include Exemestane in set I and Tamoxifen in set J due to the lack of information on the performances of Exemestane before Tamoxifen and Tamoxifen after an AI. Although BIG 1-98 trial (see Appendix C) has a setting where Tamoxifen follows Letrozole, no results were revealed about this setting.

3.1. Decision Variables

Let i and j denote the indices of the sets I and J, respectively. Our model will use the following decision variables:

y_{1i} is a binary variable indicating whether a first-step therapy i is chosen, $i \in I$;

y_{2j} is a binary variable indicating whether a second-step therapy j is chosen, $j \in J$;

$y_{z_1 i}$ is a binary variable indicating whether a first-step therapy i is extended beyond the current standard treatment period of 5 years, $i \in I$;

$y_{z_2 j}$ is a binary variable indicating whether a second-step therapy j is extended beyond 5 years, $j \in J$;

$y_{n_1 i}$ is a binary variable indicating whether a first-step therapy i is the last therapy in the schedule, $i \in I$;

$y_{n_2 j}$ is a binary variable indicating whether a second-step therapy j is the last therapy in the schedule, $j \in J$;

x_{1i} is a continuous variable denoting the duration (in years) of a first-step therapy i, $i \in I$;

x_{2j} is a continuous variable denoting the duration (in years) of a second-step therapy j, $j \in J$;

z_{1i} is a continuous variable denoting the extended duration (in years) of a first-step therapy i beyond 5 years, $i \in I$;

z_{2j} is a continuous variable denoting the extended duration (in years) of a second-step therapy j beyond 5 years, $j \in J$;

n_{1i} is a continuous variable denoting the duration (in years) of receiving nothing after a first-step therapy i, $i \in I$;

n_{2j} is a continuous variable denoting the duration (in years) of receiving nothing after a second-step therapy j, $j \in J$;

dfs is a continuous variable denoting the disease free survival (DFS) rate at the end of the treatment;

$clbc$ is a continuous variable denoting the risk of contralateral breast cancer at the end of the treatment (the meaning of "risk" in this paper is explained in the last paragraph of this subsection).

The standard treatment period for an endocrine therapy is 5 years. However, recent trials have shown that an extended therapy can prevent some of the recurrences that happen after 5 years. Actually, it was shown by Saphner et al. (1996) that,although the risk of recurrence decreases 5 years after a surgery, it does not go away. Hence, it is important to incorporate this fact in our model. Unfortunately, there are only two clinical trials that have reported results on the effectiveness of extended therapy with AIs after using 5 years of Tamoxifen. We need to make more assumptions concerning the data to get an idea about what can be a good extended therapy. We define the variables $y_{z_1 i}$, $y_{z_2 j}$, z_{2j} and z_{2j} to account for extended therapy. The necessity for defining these variables arises from the fact the risk of recurrence decreases after 5 years. Thus we will use different coefficients for the same therapy depending on whether it is used within the first 5 years or later.

Another important factor to consider is the carryover effect of therapies. In our case, it means that even if we stop the treatment the effect will be present for some time. In other words, a patient who has received a hormone therapy for a certain period of time and has not had any recurrences will have a less risk of recurrence compared to a patient who has not received any hormone therapy. Tamoxifen has been shown to have a carryover effect of at least 5 years. This effect is related to the cure achieved during the treatment. Although it has not been proven experimentally yet, we

assume that AIs will have such an effect as well. For this purpose, we define the variables $y_{n_1 i}$, $y_{n_2 j}$, n_{2j} and n_{2j}.

In addition to the above decision variables, we also introduced upper bounds on risk and slack variables for each one of the side effects. These are ub_{hf} and hf_s for hot flush risk; ub_{te} and te_s for thromboembolic event risk; ub_{cv} and cv_s for cardiovascular disease risk; ub_{vb} and vb_s for vaginal bleeding risk; ub_{fr} and fr_s for bone fracture risk; and ub_{ec} and ec_s for endometrial cancer risk. The tolerable limits on side effects are identified by experts depending on the patient's health history and preferences. By including these slacks in the objective function, we are able to choose the treatment schedule which also reduces the risk of these side effects.

It is important to note that the available trial data gives information on the percentage of patients who are disease-free, or who encountered the side effects or contralateral breast cancer. Intuitively, the higher is the percentage of patients having a particular side effect, the higher is the risk of an "average" with respect to the given side effect. So, in this paper we regard these percentages as "risks" or "chances" (for DFS).

3.2. The objective function

Our objective is to maximize the weighted sum of DFS percentage at the end of the treatment period, the negative of the risk of contralateral breast cancer, and the slack variables used in the constraints for the risks of endometrial cancer, thromboembolic events, cardiovascular diseases, bone fractures, hot flushes, and vaginal bleeding. The weights for the slack variables are scaled by the corresponding upper bounds. Based on doctors' recommendations, we formulate the following objective function (note that the importance weights can be adjusted according to the patient's preferences):

$$max \quad 5dfs - 25clbc + \frac{3}{ub_{fr}} fr_s + \frac{5}{ub_{te}} te_s + \frac{5}{ub_{cv}} cv_s + \frac{10}{ub_{ec}} ec_s + \frac{0.01}{ub_{hf}} hf_s + \frac{0.01}{ub_{vb}} vb_s \tag{1}$$

Disease-free survival (DFS) is the most important outcome of a therapy (note that the weight for DFS is lower than that for CLBC due to a considerable difference in scale of values of the corresponding variables: dfs is expected to be around 90%, while $clbc$ is usually $< 1\%$). In almost all the trial results that are published, the year by year data on the expected number of patients at risk and the number of events is given. Using this data, we observed a close to linear relationship between the duration of a therapy and the DFS percentage. Since the 5-year Tamoxifen treatment is a common arm, we are able to compare AIs with each other as well through scaling. To find the effect of Tamoxifen, we take the weighted average of all trials year by year. The weight of each trial corresponds to the number of patients attending. Using this weighted average, we scale the results of the other arms of these trials year by year again. Figure 1 shows the relation between the DFS percentage and the duration of various therapies.

As seen from this figure, a linear trend line fits the data quite well in most cases (the least-squares linear trend lines are built subject to the constraint that the line passes through the available data point at time 0). Thus, the value of DFS at the end of the treatment period is computed using the following equation:

$$dfs = 100 - \sum_i df_{1i} x_{1i} - \sum_j df_{2j} x_{2j} - \sum_i df_{z_1 i} z_{1i} - \sum_j df_{z_2 j} z_{2j} - \sum_i df_{n_1 i} n_{1i} - \sum_j df_{n_2 j} n_{2j}, \tag{2}$$

where $df_{k\cdot}$, $k \in \{1, 2, z_1, z_2, n_1, n_2\}$ denote the coefficients of corresponding variables.

Similarly, we derive the following equation for calculation of the contralateral breast cancer (CLBC) risk:

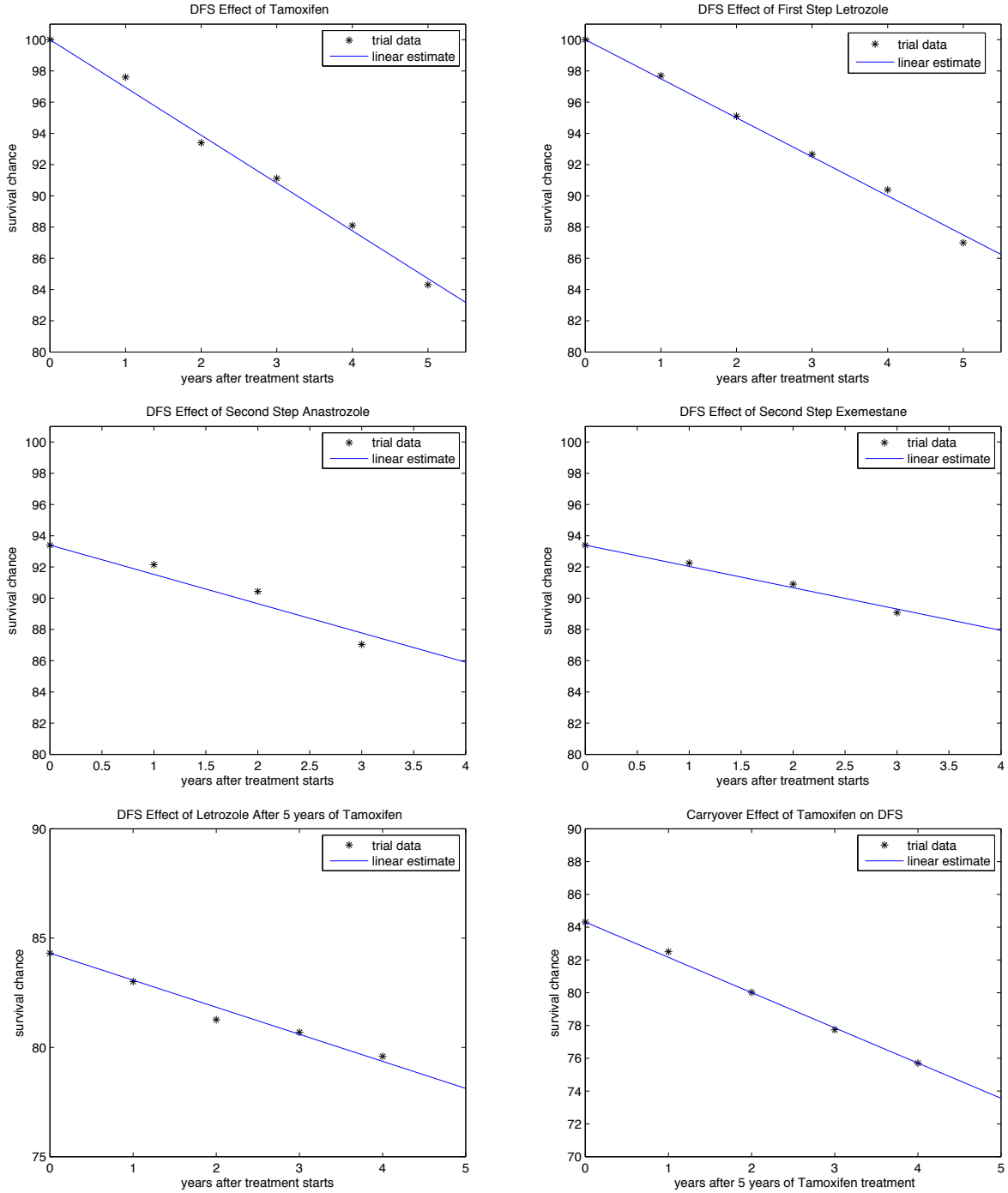

Figure 1 **The plots illustrating how DFS is effected by (a) Tamoxifen; (b) Letrozole; (c) Anastrozole after 2 years of Tamoxifen; (d) Exemestane after 2 years of Tamoxifen; (e) Letrozole after 5 years of Tamoxifen; (f) Placebo after 5 tears of Tamoxifen (carryover effect).**

$$clbc = \sum_i cl_{1i}[x_{1i} + z_{1i}] + \sum_j cl_{2j}[x_{2j} + z_{2j}], \tag{3}$$

where cl_{1i} and cl_{2j} are again the coefficients that are computed based on the linear approximations of data.

If one is interested in a treatment period beyond 5 years, some further assumptions are needed. As mentioned above, the risk of recurrence is known to decrease after 5 years. So, a smaller slope for the trend line is expected for therapies beyond 5 years, as well as the carryover effect. We have data for DFS effects of Letrozole and Anastrozole following 5 years of Tamoxifen treatment. We approximate the DFS effect of the second-step Letrozole therapy within the first five years using the ratio between the DFS effect of the second-step Anastrozole therapy within the first five years and after 5 years. In the same manner, we approximate DFS effect of a second-step Exemestane therapy after 5 years.

As seen in Figure 1 (f), the slope of the trend line is smaller for the carryover effect of 5 years of Tamoxifen compared to the slope of the trend line for the first 5 years. Assuming that the same ratio holds for actual effects of AIs for the first 5 years and their carryover effects, we approximate the DFS coefficients for n_{1i} variables. As for the coefficients of n_{2j}, we know that they have to be greater than the coefficients of z_{2j} and smaller than the coefficients of x_{2j}. We approximate these coefficients by taking the average of these. The above assumptions and approximations for extended therapy and carryover effect will not be needed if we only consider a 5-year treatment.

As for the contralateral breast cancer equation (3), we can not use the same method as DFS equation since there is no year by year data. We assume that the relation between therapy duration and CLBC risk is linear to obtain the coefficients in (3). These and the other coefficients that will be introduced in next subsection are summarized in Table 1.

Table 1 Coefficients for the MINLP model.

df_{1t_1}	3.059	$df_{z_1t_1}$	2	$df_{n_1t_1}$	2.150	cl_{1t_1}	0.134
df_{1a_1}	2.73	$df_{z_1a_1}$	1.7	$df_{n_1a_1}$	1.919	cl_{1a_1}	0.078
df_{1l_1}	2.501	$df_{z_1l_1}$	1.6	$df_{n_1l_1}$	1.758	cl_{1l_1}	0.08
df_{2a_2}	1.876	$df_{z_2a_2}$	1.405	$df_{n_2a_2}$	1.641	cl_{2a_2}	0.1007
df_{2e_2}	1.365	$df_{z_2e_2}$	1.051	$df_{n_2e_2}$	1.208	cl_{2e_2}	0.0606
df_{2l_2}	1.644	$df_{z_2l_2}$	1.237	$df_{n_2l_2}$	1.441	cl_{2l_2}	0.097
cv_{1t_1}	0.73	cv_{2a_2}	1.29	fr_{1t_1}	0.80	fr_{2a_2}	1.241
cv_{1a_1}	0.88	cv_{2e_2}	0.99	fr_{1a_1}	1.14	fr_{2e_2}	1.278
cv_{1l_1}	0.79	cv_{2l_2}	0.95	fr_{1l_1}	1.13	fr_{2l_2}	1.23
hf_{1t_1}	7.85	hf_{2a_2}	7.33	vb_{1t_1}	1.198	vb_{2a_2}	1.268
hf_{1a_1}	6.85	hf_{2e_2}	8.61	vb_{1a_1}	0.634	vb_{2e_2}	0.658
hf_{1l_1}	6.92	hf_{2l_2}	7.50	vb_{1l_1}	0.604	vb_{2l_2}	1.080

te_{1t_1}	2.1824	$te_{y_1t_1}$	0.1564	te_{2a_2}	0.13
te_{1a_1}	1.3598	$te_{y_1a_1}$	0.0974	te_{2e_2}	0.297
te_{1l_1}	0.9513	$te_{y_1l_1}$	0.0682	te_{2l_2}	0.137

3.3. Side-effect constraints

The most important constraints are the ones that are related to side effects. We consider the following side effects in our model:

- thromboembolic events;
- cardiovascular disease events;
- endometrial cancer;
- bone fractures;
- hot flushes;
- vaginal bleeding.

The data related to these side effects are available in the published results of all the trial settings (see also Figure 1). Next we introduce the constraint equations corresponding to each considered side effect.

3.3.1. Thromboembolic events Since using 5 years of Tamoxifen is a common arm in all trial settings, we use the weighted average of all settings to find the effect of Tamoxifen on thromboembolic events. The ATAC and BIG 1-98 trials give the result at the end of 5 years of Tamoxifen treatment while ITA, IES, ABCSG trial 8 and ARNO 95 report the results on the last 3 years of the 5-year treatment. Using weighted averages, the percentage of patients with thromboembolic events at the end of 5 years was 3.9%. In the last 3 years of the treatment the thromboembolic events were experienced by 1.69% of the patients. Let p_2 be the percentage of patients with thromboembolic events at the end of 2 years of Tamoxifen treatment. Then p_2 can be found from the following expression: $(100 - p_2) \times 1.69 = (3.9 - p_2)100$, yielding $p_2 = 2.248$. This shows that more thromboembolic events occur in the initial years of the treatment. We assume that the same property holds for AIs as well. Using the same ratio between the end of the 2^{nd} and the 5^{th} years, we obtain the plot shown in Figure 2. The logarithmic trend lines we use to approximate the data points capture the decreasing rate of increase in percentage of patients with thromboembolic events over time reasonably well.

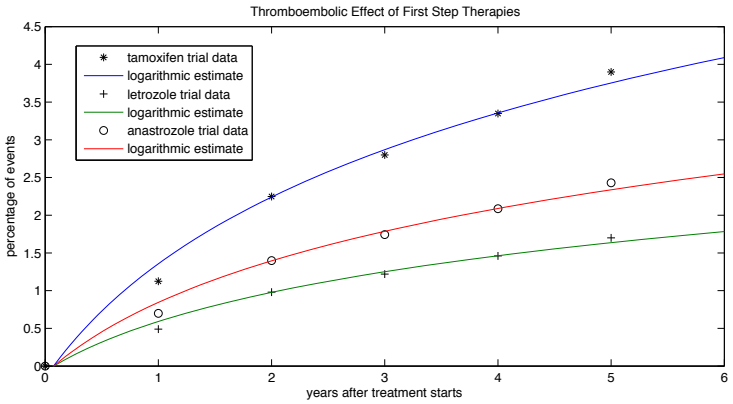

Figure 2 Thromboembolic effect of the first-step therapies.

For the second-step therapies, we assume that there is a linear relationship. This assumption is also reasonable because the risks associated with the second-step therapies are not as high as with Tamoxifen. Thus, we obtain the following constraint:

$$\sum_i te_{1i} \ln(1 + x_{1i} + z_{1i}) + \sum_i te_{y_1 i} y_{1i} + \sum_j te_{2j}[x_{2j} + z_{2j}] + te_s = ub_{te}, \tag{4}$$

where $te_{k\cdot}$, $k \in \{1, 2, y_1\}$ denote the corresponding coefficients, whose values are given in Table 1.

3.3.2. Cardiovascular diseases and bone fractures To find the effect of the therapies on cardiovascular diseases, we first approximate the effect of a 5-year Tamoxifen treatment by weighted average of the available data. Since each trial setting has a comparison between an AI and Tamoxifen, we use the corresponding ratio to calculate the effect of the AIs. Based on the trial data, we assume that the risk depends linearly on the time that the patient has been on therapy. However, the published results indicate that Tamoxifen is cardio-protective. We assume that the

longer a patient receives Tamoxifen, the less is the risk of cardiovascular diseases caused by the second-step therapies. This is expressed by the subtracted term in the following constraint:

$$\sum_i cv_{1i}[x_{1i} + z_{1i}] + \sum_j cv_{2j}[x_{2j} + z_{2j}] - 0.1x_{1t_1} \sum_j [x_{2j} + z_{2j}] + cv_s = ub_{cv}. \quad (5)$$

Tamoxifen is also known to reduce the risk of bone fractures. This fact is again expressed by the subtracted term in the equation, which restricts the risk of bone fractures by an upper bound ub_{fr}:

$$\sum_i fr_{1i}[x_{1i} + z_{1i}] + \sum_j fr_{2j}[x_{2j} + z_{2j}] - 0.1x_{1t_1} \sum_j [x_{2j} + z_{2j}] + fr_s = ub_{fr}. \quad (6)$$

The values of coefficients cv_{1i}, cv_{2j}, fr_{1i} and fr_{2j} are given in Table 1.

3.3.3. Endometrial cancer In most of the published trial results, there is no information on the incidence of endometrial cancer alone. But it is claimed that the risk caused by AIs is significantly less than the risk caused by Tamoxifen. Perhaps AIs do not increase the risk of endometrial cancer at all. On the other hand, Tamoxifen has been proven to double the risk after 1 to 2 years and quadruple at the end of 5 years. Moreover the risk does not go away after the treatment is stopped. Assuming that the risk is doubled at the end of the first year, mathematically we obtain an exponential relationship between the duration of Tamoxifen treatment and the risk for endometrial cancer, at least for the first 5 years:

$$0.5re_0 \exp(0.6931[x_{1t_1} + z_{1t_1}]) + ec_s = ub_{ec}. \quad (7)$$

Since the doctors do not recommend the duration of a Tamoxifen therapy to be more than 5 years, this equation is sufficient for our purpose. In the above equation, re_0 denotes the initial endometrial cancer risk of the patient, and ub_{ec} is an upper bound on the risk of endometrial cancer.

3.3.4. Hot flushes and vaginal bleeding Hot flushes and vaginal bleeding are not as critical as the other side effects included in our model. But since the patient will be facing these side effects almost every day over the treatment period, decreasing their incidence will definitely have a positive effect on the quality of her life. Again, based on the trial data we assume that there is a linear relationship between the risk of such events and the duration of the therapy. Moreover, the incidence of these side effects will decrease when the treatment stops. However, we are interested in limiting the maximum risk of these side effects encountered throughout the whole treatment, hence do not include the variables n_{1i} and n_{2j}, which would have negative coefficients in the corresponding constraints. We obtain the following equations:

$$\sum_i hf_{1i}[x_{1i} + z_{1i}] + \sum_j hf_{2j}[x_{2j} + z_{2j}] + hf_s = ub_{hf}, \quad (8)$$

$$\sum_i vb_{1i}[x_{1i} + z_{1i}] + \sum_j vb_{2j}[x_{2j} + z_{2j}] + vb_s = ub_{vb}. \quad (9)$$

The computed coefficients for these equations can be found in Table 1.

3.4. Scheduling constraints

The following constraints ensure that the duration of a therapy can not be greater than 0, unless it is chosen. They also enforce upper bounds on the therapy duration. Since using Tamoxifen for more than 5 years is not recommended, we set the upper bound for Tamoxifen duration to 5. For the maximum duration of AI treatments, we also set the upper bound of 5 years, however, we will test our model with the upper bound of 10 years as well.

$$x_{1i} + z_{1i} - 5y_{1i} \leq 0 \ \forall i \in I; \tag{10}$$

$$x_{2j} + z_{2j} - 5y_{2j} \leq 0 \ \forall j \in J; \tag{11}$$

$$z_{1i} - 5y_{z_1 i} \leq 0 \ \forall i \in I; \tag{12}$$

$$z_{2j} - 5y_{z_2 j} \leq 0 \ \forall j \in J; \tag{13}$$

$$n_{1i} - 5y_{n_1 i} \leq 0 \ \forall i \in I; \tag{14}$$

$$n_{2j} - 5y_{n_2 j} \leq 0 \ \forall j \in J; \tag{15}$$

As mentioned earlier, the therapies in set J are in effect only if they are used after Tamoxifen. The following set of constraints guarantees this:

$$y_{2j} - y_{1t_1} \leq 0 \ \forall j \in J. \tag{16}$$

The next constraint ensures that after a first step treatment, the patient either receives nothing or a second step therapy,or has an extended therapy with the same drug:

$$y_{n_1 i} + y_{z_1 i} + \sum_j y_{2j} \leq 1 \ \forall i \in I; \tag{17}$$

The following set of constraints guarantees that in order to extend a therapy or do nothing to see its carryover effect, the therapy must be chosen first:

$$y_{n_1 i} - y_{1i} \leq 0 \ \forall i \in I; \tag{18}$$

$$y_{n_2 j} - y_{2j} \leq 0 \ \forall j \in J; \tag{19}$$

$$y_{z_1 i} - y_{1i} \leq 0 \ \forall i \in I; \tag{20}$$

$$y_{z_2 j} - y_{2j} \leq 0 \ \forall j \in J; \tag{21}$$

The following constraints ensure that if a therapy is chosen then it must be used for at least τ years. This minimum duration can be adjusted according to the preferences of experts. We used the values of τ in the range between 0.5 and 2 years.

$$x_{1i} + z_{1i} - \tau y_{1i} \geq 0 \ \forall i \in I; \tag{22}$$

$$x_{2j} + z_{2j} - \tau y_{2j} \geq 0 \ \forall j \in J. \tag{23}$$

The next set of constraints ensures that the total duration of the chosen therapies is equal to the treatment period, which is denoted by p ($p \leq 10$).

$$\sum_i x_{1i} + \sum_j x_{2j} = 5; \tag{24}$$

$$\sum_i [z_{1i} + n_{1i}] + \sum_j [z_{2j} + n_{2j}] = p - 5. \tag{25}$$

We can choose exactly one therapy from set I and at most one therapy from set J. This is guaranteed by:

$$\sum_i y_{1i} = 1; \tag{26}$$

$$\sum_j y_{2j} \leq 1. \tag{27}$$

4. Test Results

To summarize, the complete formulation of our model is given by the objective (1) subject to the constraints (2)–(27), where

$$y_{1i}, y_{2j}, y_{z_1 i}, y_{z_2 j}, y_{n_1 i}, y_{n_2 j} \in \{0,1\} \quad \forall i \in I, \quad \forall j \in J,$$

$$x_{1i}, x_{2j}, z_{1i}, z_{2j}, n_{1i}, n_{2j} \geq 0 \quad \forall i \in I, \quad \forall j \in J,$$

and the coefficients are given in Table 1. We ran our model using BARON solver available from NEOS server NEOS (2008) for 11 different testing scenarios. The considered instances were sufficiently small to be solved to optimality within a few seconds of CPU time on a modern PC. The average solution time is 0.005sec where the average number of iterations is 2.636. The treatment duration and used values for the upper bounds on the percent of increase of the side effect risks for each scenario are given in Table 2 (again, these values can be adjusted according to preferences of a particular patient or a doctor).

Table 2 The parameter values used in the experiments.

Scenario	p	re_0	ub_{te}	ub_{cv}	ub_{fr}	ub_{ec}	ub_{hf}	ub_{vb}
1-4	5	0.04	10	10	10	0.1	50	10
5	5	0.04	10	10	4.6	0.1	50	10
6	5	0.04	10	3.64	10	0.1	50	10
7	5	0.04	3	10	10	0.1	50	10
8	10	0.04	10	10	10	0.1	50	10
9	10	0.04	20	20	20	0.1	100	20
10	8	0.04	20	20	20	0.1	100	20
11	10	0.04	20	20	7	0.1	100	20

4.1. Standard treatment

In the first set of experiments, we considered a standard treatment period of 5 years (scenarios 1–7). The first 4 scenarios differ only by the lower bound τ on the duration of a therapy, while scenarios 5–7 use $\tau = 2$ and a smaller than usual upper bound on the percent of increase of risk associated with one of the side effects (bone fracture for scenario 5, cardiovascular disease for scenario 6, and thromboembolic events for scenario 7).

Table 3 shows the values of τ and solution of our model for all 7 testing scenarios. The optimal schedule for scenarios 1–4 is to use Tamoxifen for the first τ years and then Exemestane for the remaining $5 - \tau$ years. We can conclude that as soon as the patient can tolerate all the side effects given in the solution tables it is better to switch to Exemestane after initial Tamoxifen.

The side effects that can become intolerable with decreasing duration of Tamoxifen therapy are cardiovascular diseases, bone fractures and hot flushes, as we observe increase in risk of these side effects when τ decreases.

We use the minimum duration of a therapy $t = 2$ in scenarios 4–6. In scenario 5, we decreased the upper bound ub_{fr} on the bone fracture risk from 10% to 4.6%, since, especially for old people, fractures can cause serious problems. In this case, our model recommends to use Tamoxifen for about 26 months and then to switch to Letrozole for the remaining 34 months. Similarly, in scenario 6 the upper bound on the cardiovascular disease risk is decreased from 10% to 3.64%. The resulting schedule is to use Tamoxifen for about 27 months and then to switch to Letrozole for the remaining 33 months. Finally, if the upper bound on the risk of thromboembolic events is changed from 10% to 3%, the recommendation is to use Letrozole for all 5 years of treatment.

Table 4 shows the upper bounds on the side effects on which the solution changes. These values are obtained by experimentation. We observe that sequencing Tamoxifen and Exemestane is best in terms of disease-free survival chance. If there is more concern about the anticipated side effects either sequencing Tamoxifen and Letrozole or a monotherapy with Letrozole is recommended.

Table 3 **Values of τ and MINLP model solution for the seven considered 5-year treatment scenarios. An optimal schedule for scenarios 1-4 consists of τ years of Tamoxifen therapy followed by $5-\tau$ years of Exemestane therapy. For the remaining scenarios, we have the following schedules: 2.176 year of Tamoxifen and 2.824 years of Letrozole (scenario 5); 2.236 years of Tamoxifen and 2.764 years of Letrozole (scenario 6); and 5 years of Letrozole (scenario 7).**

Scenario	1	2	3	4	5	6	7
τ	2	1.5	1	0.5	2	2	2
DFS chance	89.787	90.634	91.481	92.328	88.701	88.616	87.61
CLBC risk	0.45	0.413	0.376	0.34	0.565	0.568	0.4
Thromboembolic event risk	3.132	2.883	2.544	2.065	2.752	2.785	1.636
Cardiovascular disease risk	3.83	4.035	4.29	4.595	3.657	3.64	3.95
Bone fracture risk	4.834	5.148	5.512	5.926	4.6	4.57	5.65
Hot flush risk	41.53	41.91	42.29	42.67	38.261	38.283	34.6
Vaginal bleeding risk	4.37	4.1	3.83	3.56	5.657	5.66	3.02
Endometrial cancer risk	0.08	0.057	0.04	0.028	0.09	0.094	0.04

Table 4 **Sensitivity analysis. The UB* values are the values on the upper bounds of side effects at which point the main decision of which drugs to sequence changes. Duration of each drug further depends on the upper bound within the interval on which it is recommended.**

	UB*	solution if UB $<$ UB*	solution if UB $\geq$ UB*
Thromboembolic event risk	3.13223	5L	2T+3E
Cardiovascular disease risk	3.72445	2T+3L	2.32T+2.68E
Bone fracture risk	4.65821	2T+3L	2.32T+2.68E
Endometrial cancer risk	0.0799	5L	2T+3E

It is important to note that AIs in general perform better in terms of DFS if they are sequenced after Tamoxifen compared to the situation where they are used upfront. It is not unreasonable to think that Tamoxifen causes some changes in the body that help AIs to perform better. A natural question is the duration of a Tamoxifen therapy that will yield such an effect. In our experiments, we assume that this effect can already be felt in τ years.

Note that some of the obtained optimal schedules coincide with the actual treatment plans in trials whose results were used to develop our model (these trial results are summarized in

Table 5). Namely, our output schedules from scenarios 1 and 7 are exactly the plans 2T+3E and 5L. Comparing the corresponding figures in Tables 3 and 5, we conclude that our model describes the real-life data reasonably well. Moreover, the results of our experiments suggest the effectiveness of these two treatment schedules used in practice and yield additional plans that may prove to be useful in real life.

Table 5 **Scaled end point data obtained from the published trial results for five different 5-year treatments (see Appendix C for more detail). The first three treatments are 5-year Tamoxifen, Anastrozole and Letrozole therapies, respectively, while the last two combine two years of Tamoxifen with 3 years of Anastrozole and Exemestane, respectively.**

	5T	5A	5L	2T+3A	2T+3E
DFS chance	84.312	86.351	87.005	87.040	89.081
CLBC risk	0.67	0.39	0.4	0.57	0.45
Thromboembolic event risk	3.9	2.43	1.7	2.65	3.16
Cardiovascular disease risk	3.64	4.39	3.93	4.73	3.84
Bone fracture risk	3.99	5.7	5.66	4.72	4.83
Hot flush risk	39.26	34.27	34.62	37.69	41.55
Vaginal bleeding risk	5.99	3.17	3.02	6.2	4.37

Finally, to verify whether the set of trial schedules used to generate the data in Table 5 can be "dominated" by a single schedule, which would have lower risk for any of the side effects, we attempted to solve our model by setting the upper bounds for side effect risks to the lowest value in the corresponding row of the table. The resulting MINLP appeared to be infeasible.

4.2. Extended treatment

In the second set of experiments, we tried our model for extended treatment periods of up to 10 years. We considered 4 different extended treatment scenarios (scenarios 8–11 in Table 2). We used the value of $\tau = 2$ in all 4 scenarios. The corresponding results are reported in Table 6. For

Table 6 **Results for extended treatment scenarios.**

Scenario	8	9	10	11
DFS chance	83.762	84.532	86.634	84.071
CLBC risk	0.45	0.753	0.632	1.032
Thromboembolic event risk	3.132	4.617	4.023	3.729
Cardiovascular disease risk	3.83	7.78	6.2	5.417
Bone fracture risk	4.834	10.224	8.068	7.00
Hot flush risk	41.53	84.58	67.36	58.83
Vaginal bleeding risk	4.37	7.66	6.344	5.692
Endometrial cancer risk	0.08	0.08	0.08	0.08

extended therapy, we observe that side effects become more significant in determining an effective schedule. This is due to the carryover effect as well as the decreased risk of recurrence after 5 years. If the patient had gone through a very effective therapy for the first 5 years, she may not need any further endocrine therapy, since an extended treatment would only increase the side effects while contributing very little to the increase of DFS chance. In particular, an optimal schedule for scenario 8 is to use Tamoxifen for 2 years, then use Exemestane for 3 years, and do nothing for the remaining 5 years. Therefore, in order to extend the treatment beyond 5 years, we increase the weight of DFS by increasing the coefficient of dfs from 5 to 15 in the objective (1), while

doubling most of the upper bounds on increase of the side effect risks in scenarios 9–11. With such an increase in the coefficient, the solution for scenario 9, which is to use Tamoxifen for 2 years and then Exemestane for 8 years, remains the same even if we remove all slack variables of side effect constraints from the objective. In scenario 10, we reduce the therapy duration to 8 years. This yields a solution similar to the previous scenario; use Tamoxifen for 2 years and then Exemestane for 6 years. Finally, scenario 11 is for a 10-year treatment with $ub_{fr} = 7\%$ and the remaining upper bounds the same as in scenario 10. The solution is to use Tamoxifen for 2 years, Exemestane for 5.009 years, and nothing for the remaining time.

In general, with tighter upper bounds on side effects, the model suggests to continue Exemestane therapy after 2 years of Tamoxifen until the corresponding upper bound on the increase in risk is achieved, at which point the therapy is discontinued. But if the upper bounds do not even allow to use Exemestane within the first 5 years, then the model recommends different schedules. For example, if we set $u_{cv} = 3.64$, then the model recommends to use use Tamoxifen for 27 months, Letrozole for 33 months and nothing for the remaining time period.

Another interesting observation based on our model estimates is that, since Exemestane performs much better than any other AI as a second step therapy in terms of DFS chance, its carryover effect and its effect after 5 years are also significantly better than that of the others. Although in some schedules the patient uses some drugs for the whole treatment period without violating the upper bound constraints, the DFS chance for such a schedule is considerably lower than that achieved by switching to Exemestane and stopping the treatment earlier, provided that switching to Exemestane does not violate any upper bound within the first 5 years.

In all considered examples, we used an upper bound of 10 years for the duration of AIs. When we test the same examples with an upper bound of 5, we observe that the solution does not change in terms of recommending to switch to Exemestane after 2 years of Tamoxifen, and then continuing the Exemestane therapy as long as possible (until a side effect constraint is violated or the duration of the Exemestane therapy exceeds 5 years).

5. Conclusion

Using the data from published trial results, we build a MINLP model to find efficient endocrine therapy schedules for Hr+, early stage breast cancer patients who are postmenopausal. Since two-thirds of breast cancer patients have tumors that are Hr+, optimized hormone therapy schedules are of great importance. Depending on patient information such as age, health history and cancer stage, different treatment schedules can be effective for different patients. Nowadays, it is also extremely important to inform the patient about available treatment options and take into account her opinions in the decision making process. Thus, the treatment schedule may change for each patient according to her personal preferences as well. These are important factors that need to be taken into account when optimizing treatment schedules. However, the current availability of data is not sufficient to account for all these parameters. Our model completely relies on the available data, therefore availability of additional accurate data could help to improve the estimates of model parameters as well as to build more sophisticated models that will account for patient-specific information. As of now, our model can incorporate the differences of patients from one another by adjusting importance weights and tolerability constraints for side effects which are to be identified by the patient and her doctor.

As mentioned earlier, very little work has been done in optimizing the hormone therapy for breast cancer. To best of our knowledge, the model proposed in this paper is the first OR model that incorporates the side effect constraints in determining efficient schedules. Although results for different schedules are reported in some clinical trials, there is no agreement on what schedules are most effective in the medical community. This work is an attempt to utilize OR techniques in order to help doctors and patients in their decision making process.

The MINLP model suggests to use Tamoxifen first and then switching to Exemestane as long as the patient can tolerate the anticipated side effects. Especially for patients who have higher risks of cardiovascular diseases or fractures, it is better to switch to Letrozole after initially using Tamoxifen. For patients with higher risks of thromboembolic events and endometrial cancer, our model suggests to use a mono therapy with Letrozole. The durations of the therapies depend on the side effect tolerability constraints. It is important to remember that our observations are for an "average" patient. Although Anastrozole is not included in any of the solution schedules we obtained, it can still be an effective therapy for some patient subgroups. As we get more information on the effects of therapies on patient subgroups, we can adjust our model accordingly. Another important observation was made regarding the long term impact of treatment schedules. Right now, the standard treatment period for hormone therapy is five years. Recent studies suggested that if the patient received Tamoxifen for the first five years then it is better for her to continue the treatment with an AI. Based on our assumptions stated, we observed that if the patient has a really efficient treatment for the first five years she may prefer to discontinue the treatment after the five years. This can be explained by arguing that even though a continued treatment can slightly decrease the risk of recurrence, the associated side effect risks may outweigh the potential gain.

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Appendix A: Cancer Stages

In this section we will give a summary of cancer stages. The stage of the cancer is the most important factor in determining the treatment plan. Staging is the process of finding out how widespread a cancer is. A staging system is a standardized way to summarize information about how far a cancer has spread. The most common system used to describe the stages is the American Joint Committee on Cancer ($AJCC$) TNM System American Cancer Society (2006), where

- T is the tumor size and spread;
- N is the spread to lymph nodes;
- M is the metastasis, which is the spread to distant organs.

Table 7 describes the T, N, M categories, and Table 8 provides a summary of cancer stages and 5-year relative survival rates (relative with respect to the survival rates of people without breast cancer) of each stage depending on the patient data diagnosed from 1995 to 1998.

Appendix B: Trial Settings

1. 5 years of Tamoxifen or 5 years of Anastrozole (ATAC Trial)
2. 2-3 years Tamoxifen first, next either 2-3 years Anastrozole or Tamoxifen such that the whole therapy lasts for 5 yrs (ITA Trial, ABCSG trial 8 and ARNO 95 trial)
3. 2 years Tamoxifen first, next either 3 years Exemestane or Tamoxifen (IES Trial)
4. 5 years of Letrozole or 5 years of Tamoxifen (BIG 1-98 Trial)
5. 5 years of Tamoxifen followed by either 5 years of Letrozole or nothing (placebo)(MA-17 Trial)
6. 2 years of Tamoxifen given in conjunction with the first-generation AI aminoglutethimide followed in turn by 3 years of Tamoxifen alone or 5 years of Tamoxifen. (ABCSG-6 trial from the Austrian Breast and Colorectal Cancer Study Group)
7. Patients free of recurrence through 5 years of the above treatment (ABCSG-6) either have 3 years of Anastrozole or placebo. (ABCSG-6a trial)
8. 5 years or more Tamoxifen (ATLAS, ATOM trials)
9. 5 years of Tamoxifen followed by either 5 years of Exemestane or nothing (placebo) (NSABP B-33) (based on the results of MA-17 this trial was discontinued and participants taking placebo were offered Exemestane)
10. Comparison of two AIs, Exemestane and Anastrozole as first-line adjuvant therapy (MA-27)

Table 7 T,N **and** M **categories**

T categories	**N categories**	**M categories**
TX: Primary tumor cannot be assessed	**NX**: Regional lymph nodes cannot be assessed	**MX**: Presence of distant spread (metastasis) cannot be assessed
T0: No evidence of primary tumor (this sometimes happens)	**N0**: Cancer has not spread to regional lymph nodes	**M0**: No distant spread
Tis: Carcinoma in situ; intraductal carcinoma, lobular carcinoma in situ, or Paget disease of the nipple with no associated tumor mass	**N1**: Cancer has spread to 1 to 3 axillary lymph node(s)	**M1**: Distant spread is present
T1: Tumor 2 *cm* (4/5 of an inch) or less in greatest dimension	**N2**: Cancer has spread to 4 to 9 lymph nodes	
T2: Tumor more than 2 *cm* but not more than 5 *cm* (2 inches) in greatest dimension	**N3**: Cancer has spread to 10 or more axillary lymph nodes	
T3: Tumor more than 5 cm in greatest dimension		
T4: Tumor of any size growing into the chest wall or skin		

Table 8 **Cancer Stages based on** TNM **system and 5-year survival rates**

Stage	TNM category	5-year relative survival rate
0	Tis, N0, M0	100
1	T1, N0, M0	100
2A	T0, N1, M0 **or** T1, N1, M0 **or** T2, N0, M0	92
2B	T2, N1, M0 **or** T3, N0, M0	81
3A	T0-2, N2, M0 **or** T3, N1-2, M0	67
3B	T4, N0-2, M0	54
3C	T0-4, N3, M0	NA
4	T0-4, N0-3, M1	20

Appendix C: Brief summary of published trial results

ATAC (5 years Tamoxifen vs 5 years Anastrozole)

Median follow up for this trial is 68 months. 5216 patients were enrolled in this trial. The simplest interpretation of the results is that Anastrozole prevents one in four of the relapses seen in patients on Tamoxifen. This

yields highly significant improvements in disease-free survival, recurrence-free survival and distant disease-free survival. During the first 2 years of treatment, both trial arms had a similar overall QoL (Quality of Life) impact Fallowfield et al. (2004). At the end of the treatment, endometrial cancer, thromboembolic events, hot flushes and hysterectomy were seen less in Anastrozole group compared with Tamoxifen group, while the latter had benefits in terms of causing less fractures and osteoporosis. The first results of the endometrial sub-protocol following 2 years of treatment was published recently Duffy et al. (2006). After 2 years of Anastrozole treatment, endometrial thickness remained $\leq$5 mm whereas in patients receiving Tamoxifen, endometrial thickness increased by 3.2 mm to 7.0 mm. At the end of 2 years, the number of patients exhibiting endometrial histopathology were 5.1 and 17.9 percent in the Anastrozole and Tamoxifen group, respectively. Although the difference is not statistically significant, which is likely to be because of insufficient number of patients (285) recruited for this sub-protocol, the results are still valuable.

ITA (5 years of Tamoxifen vs switching to Anastrozole after 2-3 years of Tamoxifen)

Median follow up for this trial is 36 months. 448 patients were enrolled. All the patients were already receiving Tamoxifen and they were randomly assigned to either switching Anastrozole or continuing Tamoxifen. The preliminary results are published in Boccardo et al. (2005). Disease-free and local recurrence-free survival were significantly longer in the Anastrozole group. Although there were more side effects recorded in the Anastrozole group, more events were life threatening or required hospitalization in the Tamoxifen group.

ABCSG trial 8 and ARNO 95 trial (5 years of Tamoxifen vs switching to Anastrozole after 2 years of Tamoxifen)

Median follow up for these trials is 28 months and there were 3224 enrolled. The patients who had completed 2 years of Tamoxifen treatment were randomized to switch receiving Anastrozole or continue receiving Tamoxifen. The results are published in Jakesz et al. (2005). There was a 40% decrease in the risk for an event in the Anastrozole group as compared with the Tamoxifen group where an event is described as local or distant metastatis, or contralateral breast cancer. Both treatments were well tolerated while significantly more fractures and significantly less thromboses were recorded in the Anastrozole group.

IES (5 years of Tamoxifen vs switching to Exemestane after 2-3 years of Tamoxifen)

Median follow up for this trial is 30.6 months. There were 4742 patients enrolled. The results are published in Coombes et al. (2004). A 32% reduction in risk was observed in terms of disease free survival in Exemestane group compared with the Tamoxifen group. Severe side effects of Exemestane were rare. According to the quality of life results Fallowfield et al. (2006), the switch to Exemestane neither increased nor decreased endocrine symptoms present after 2 to 3 years of Tamoxifen; the switch did not also initiate significant reports of new symptoms. The results indicate that the clinical benefits of switching to Exemestane over continuing with Tamoxifen are achieved without significant detrimental effect on quality of life.

BIG 1-98 (5 years of Tamoxifen vs 5 years of Letrozole)

The median follow-up of this trial is 25.8 months and there were 8010 patients enrolled. The results are published in The Breast International Group (BIG) 1-98 Collaborative Group (2005).There are four arms of this trial: Letrozole, Letrozole followed by Tamoxifen, Tamoxifen and Tamoxifen followed by Letrozole. The analysis in The Breast International Group (BIG) 1-98 Collaborative Group (2005) compares only the two groups assigned to receive Letrozole initially with the two groups assigned to receive Tamoxifen initially. For this reason, although an AI followed by Tamoxifen is an interesting setting, we do not have any data. As compared with initial Tamoxifen, initial Letrozole significantly reduced the risk of events which are included in the definition of disease-free survival. The risk of distant recurrence was also significantly reduced by Letrozole. While the side effects such as thromboembolism, endometrial cancer and vaginal bleeding are more common in the Tamoxifen group, there is a higher incidence of skeletal and cardiac events and of hypercholesterolemia in the Letrozole group.

MA.17 (5 years of Tamoxifen followed by Letrozole or Placebo)

Most recurrences in women with breast cancer receiving 5 years of adjuvant Tamoxifen occur after 5 years Goss et al. (2005). This trial was designed to determine if extended adjuvant hormone therapy with Letrozole reduces the risk of such recurrences or not. The median follow-up of this trial is 30 months and there were 8010 patients enrolled. The results are published in Goss et al. (2005). Women receiving Letrozole had longer DFS and distant DFS compared to the group receiving placebo. Overall survival is the same in both arms but it was improved with Letrozole for the patients who has node positive tumors. The Letrozole

arm experienced more hormone-related side effects. The incidences of bone fractures and the cardiovascular events were the same. This result give some idea about the carryover effect of Tamoxifen on cardiovascular events and fractures. As we mentioned Section 3, Tamoxifen has some advantages over AIs in terms of cardio protective effect and decreasing the risk of fractures and bone loss. By considering the results of the BIG 1-98 trial, we can say that either Letrozole does not have a negative effect on fractures and cardiovascular diseases or using Tamoxifen for 5 years helps to decrease the risk of fractures and cardiovascular diseases even after it is stopped.

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