UNIVERSITY OF CALGARY

Treatment Options in Locally Advanced Breast Cancer

by

Dr. Daran Lea Austen

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR

THE DEGREE OF MASTER OF SCIENCE

DEPARTMENT OF COMMUNITY HEALTH SCIENCES

Calgary, Alberta

May, 2003

UNIVERSITY OF CALGARY

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the faculty of Graduate Studies for acceptance, a thesis entitled "Treatment Options in Locally Advanced Breast Cancer" submitted by Dr. Lea Austen in partial fulfillment of the requirements for the degree of Master of Science, Epidemiology.

Linda S. Cook

Supervisor, Dr. Linda Cook, Department of Community Health Sciences

Dr. Penny Brasher, Department of Community Health Sciences

Mr. Robert Lee, Department of Community Health Sciences

Internal External Examiner, Dr. S. Gluck, Department of Medical Science

May 8, 2003

Date

ABSTRACT

Objectives: A primary objective of this study is to describe survival outcomes among a cohort of women treated for locally advanced breast cancer (LABC) with respect to multimodality treatment type. Another primary objective is to define and describe a preliminary framework for a decision analysis model for the treatment of patients with LABC.

Design: I. Retrospective Cohort study utilizing Survival Analysis methodology (Kaplan Meier estimates and Cox Proportional Hazards model)

II. Decision Analysis Model Development

Setting: Alberta Population based cancer registry and database

Patients: Women of all ages, treated in the province of Alberta, diagnosed with LABC during the years 1994-1996, with no previous invasive cancer diagnosis will be included in the study.

Conclusion: Breast cancer survival in LABC patients is related to disease stage, histological grade, and use of hormone therapy; no treatment modalities were predictive of survival. The use of neo-adjuvant chemotherapy versus standard therapy did not predict survival when other factors were considered. Breast conserving techniques were used more frequently after neo-adjuvant chemotherapy than standard therapy; no differences in survival between breast conserving therapies and mastectomy were identified. The framework for a decision analysis model for treatment options in LABC was developed and described.

ACKNOWLEDGEMENTS

Dr. L. Cook
Mr. R. Lee
Dr. P. Brasher
Dr. S. Gluck
Staff and Students, Department of Community Health Sciences, University of Calgary

TABLE OF CONTENTS

LIST OF TABLES

[1] LABC: Locally Advanced Breast Cancer

LIST OF FIGURES

[2] LABC: Locally Advanced Breast Cancer

[2] LABC: Locally Advanced Breast Cancer

I. Introduction

Breast cancer is an important health concern for women; it was the leading type of new cancer diagnosis and second leading cancer cause of death for women in 2001 [1]. Five to fifteen percent of new breast cancer cases in the United States [2], and ten to twenty nine percent of patients worldwide [3], are first seen with large tumors (greater than 3 cm) and/or palpable lymph nodes, considered locally advanced disease. The treatment of locally advanced breast cancer (LABC) with various combinations of surgery, radiotherapy, and chemotherapy, i.e. multimodality therapy, has been accepted since the 1980's. There is controversy over the use, sequence and benefit of the various treatment modalities. The effect of chemotherapy given prior to surgery (neo-adjuvant), on overall and breast cancer specific survival is uncertain when compared to chemotherapy given after surgery (adjuvant). The role of surgery and radiotherapy in patients who have a dramatic and complete response to neo-adjuvant chemotherapy is also unclear. The role of breast conserving therapies in patients with LABC has not been determined.

II. Study Objectives and Rationale

The overall objective of this study is to provide supporting data and statistical analyses to help inform decisions regarding treatment options for patients with locally advanced breast cancer (LABC).

The specific objectives of the proposed study are to:

1. Describe survival outcomes among women of all ages treated for LABC in the province of Alberta diagnosed in the years 1994-1996 with respect to multimodality treatment type and predictive factors.
2. Define and describe an approach and a preliminary framework for a decision analysis model targeted towards identification of preferred strategies for the treatment of patients with LABC.

This research will provide some quality assurance and feedback regarding the impact of treatments for LABC to practitioners and patients in Alberta, and generally any others treating patients with LABC. It will also provide a modelling framework that can be used to determine the utility of decisions regarding various treatment options in LABC.

III. Background

A. Definition of Locally Advanced Breast Cancer

The definition of LABC has changed over the years as different staging systems have been developed and new prognostic implications have been examined. The most recent American Joint Commission on Cancer (AJCC) tumor-lymph nodes-metastasis (TNM) staging system is the most widely accepted and is used in the majority of research papers (See Figure 1). Historically, LABC was considered AJCC stage IIIA and IIIB; many recent reports have extended this definition to include any tumors greater than 3 centimetres (cm) in size [4-16]. Inclusion of tumors of this size reflects the potential importance of breast conserving surgery, as tumors greater than 3 cm in size are less amenable to breast conserving surgeries. There is also a correlation between the size of the tumor and the incidence of lymph node metastasis, which is a recognized prognostic factor [2]. Thus, a current definition of LABC that will be used in this study is an invasive carcinoma greater than 3 cm in maximum dimension and/or tumors with fixed or matted axillary lymphadenopathy (AJCC, N2 or N3) in the absence of metastatic disease.

B. History of Treatment for Locally Advanced Breast Cancer

Literature on the treatment of LABC dates back to Haagensen and Stout who reported results of 1135 patients treated between 1915 and 1942 [17]. Radical mastectomy, as described by Halstead [18], was the treatment of choice for breast cancer in their series. They described a group of patients with "grave signs" who had poor outcomes. The signs included skin ulceration, chest wall fixation, and axillary lymph nodes greater than 2.5 cm or matted together. Patients with 2 or more signs had a 42% local recurrence and 2% 5-year survival with radical mastectomy.

Figure 1 - American Joint Commission on Cancer (AJCC) Tumor-Nodes-Metastasis (TNM) Classification of Breast Carcinoma

(Adapted from The M.D. Anderson Surgical Oncology Handbook, 1995)[19]

Primary Tumor (T)

- T0 – No evidence of primary tumor
- Tis – Carcinoma in-situ (non-invasive)
- T1 – Tumor less than or equal to 2 cm in greatest dimension
- T2 – Tumor greater than 2 cm but less than or equal to 5 cm
- T3 – Tumor greater than 5 cm
- T4 – Any size tumor with direct extension to chest wall or skin

Regional Lymph Nodes (N)

- N0 – No regional lymph node metastases
- N1 – Metastasis to mobile ipsilateral axillary lymph nodes
- N2 – Metastasis to ipsilateral axillary lymph nodes fixed to one another or other structures
- N3 – Metastasis to ipsilateral internal mammary lymph nodes

Distant Metastasis (M)

- M0 – No distant metastasis
- M1 – Distant metastasis (includes ipsilateral supraclavicular node(s))

Disease Stage Grouping

Disease Stage	*Tumor (T)*	*Nodes (N)*	*Metastasis (M)*
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIa	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIb	T2	N1	M0
	T3	N0	M0
Stage IIIa	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1, N2	M0
Stage IIIb	T4	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

Other more recent reports have looked at the use of surgery alone for LABC and reported local recurrence rates as high as 50% and 10 year survival of 22-29% in heterogeneous populations [20-22]. A review of surgical outcomes by Fracchia et al. [22] showed that the presence of nodal disease carried a 10-year survival of 21%, compared to 75% in node negative patients. It is clear that surgery alone is unlikely to be curative in LABC due to the systemic nature of the disease.

Given the poor outcome of patients treated with radical mastectomy, other forms of treatment have been tried. A report from M.D. Anderson Cancer Centre in 1965 [23] reported the results of local radiotherapy for LABC. They suggested a 30% local recurrence rate, but a 5-year survival of only 25%. Another report on the use of radiation therapy alone showed a local recurrence rate of 46%, and 5-year survival of 30% [24]. The National Cancer Institute in Milan, Italy published their results of radiotherapy in 1976 [25]. They reported similar local recurrence rates and a 21% 5-year survival. Again, treatment with only one type of local therapy has typically failed to address the systemic nature of the disease.

C. Unimodality versus Multimodality Treatments

The treatment strategies for LABC can be classified into unimodality (i.e. single mode) and multimodality (i.e. more than one mode in sequence or simultaneous) based on the use of surgery, chemotherapy and radiation therapy. In order to address both the local and systemic nature of breast cancer, treatments and outcome studies have focused on multimodality approaches. Several randomized controlled trials have compared unimodality therapy versus multimodality therapy for LABC [23, 26-30]. Caceres [23] reported, abstract only, a randomized controlled trial comparing three treatment arms for LABC. The three arms of the study were radiation therapy, radiation therapy plus surgery, and radiation therapy plus chemotherapy. The study reported median survival of 24.6 months for the radiation therapy plus chemotherapy arm, 19.9 months for the radiation therapy only arm, and 17.8 months for the radiation therapy plus surgery arm. Grohn [26], and Klefstrom [27] in an update of the Grohn study, reported a randomized trial of 119 patients with LABC. All patients had a modified radical mastectomy, surgery to remove the entire breast and axillary lymph

nodes only. Patients were then treated with radiation therapy versus chemotherapy versus both radiation therapy plus chemotherapy. Five-year disease free survival was 22% for radiation therapy, 30% for chemotherapy, and 67% for radiation therapy plus chemotherapy ($p < 0.001$). The European Organization for Research and Treatment of Cancer (EORTC) breast cancer group reported a four arm randomized controlled trial comparing (n=363): 1) radiation therapy, 2) radiation therapy plus hormone therapy (Tamoxifen), 3) radiation therapy plus chemotherapy, and 4) radiation therapy plus hormone therapy plus chemotherapy [29]. They reported a significant increase in time to local/regional recurrence with the radiation therapy plus hormone therapy plus chemotherapy group, (5-year recurrence was 29%, 48%, 53%, and 64% for each group (1-4 as above) (log rank, $p < 0.001$). They did not show an increase in overall survival (log rank, $p = 0.115$) between the four groups (5-year survival was 36%, 34.5%, 32%, and 55% for groups 1-4). Derman [30] reported a non-significant trend of increased overall median survival in pre-menopausal women with stage III disease given combined local therapy and adjuvant chemotherapy versus local therapy only (63 versus 49 months) ($p=0.24$). These studies highlight the trend of increased survival for patients with LABC treated with multimodality therapy.

D. Multimodality Treatment in Locally Advanced Breast Cancer

Although it seems clear from the historical evidence that there is a need to address both the local and systemic nature of LABC, the preferred treatment strategies have yet to be determined. Since the early 1980's, efforts have been focused on multimodality approaches to the treatment of LABC by combining surgery, radiation therapy and systemic chemotherapy in different combinations. The treatment program used for any single patient will depend on a number of factors, including:

1. Tumor/disease factors – size, location, histology and pathologic factors
2. Patient factors – issues such as general health status and presence of other health problems, geographic location, time availability, travel
3. Patient preference – the patient may have a preference for a particular treatment program
4. Physician/institution preference – which may represent local practice patterns, experience/comfort with certain forms of treatment, budget, available resources, geographic location.

Despite the complexity of individual treatment decisions, there appear to be certain fundamental treatment strategies. The need for local control is achieved by the use of surgery, radiation therapy or a combination of the two modalities. The need for systemic treatment is achieved by the addition of multi-drug chemotherapy.

With reference to the problem of treatment for LABC, this paper will limit the perspective to that of the patient and will assume that the physician acts in the best interest of the patient. As we have identified, the decision regarding treatment for LABC is complex and much of the uncertainty involves issues surrounding the sequence and type of multimodality treatment for LABC that maximize positive consequences (i.e. survival and quality of life) while minimizing negative consequences (i.e. death, recurrence, and complications).

There remain a number of key decisions that a patient and physician need to make with respect to treatment. These include the use of neo-adjuvant chemotherapy (chemotherapy given before surgery); the use of surgery or radiation therapy for local control in patients who have a complete response (no identifiable tumor remaining) after neo-adjuvant chemotherapy; and the type of surgery to consider, mastectomy (removal of all breast tissue on the affected side) or segmental mastectomy (removal of only a portion of the breast tissue around the tumor).

1. Neo-Adjuvant versus Adjuvant Chemotherapy

A number of randomized studies have been reported comparing neo-adjuvant and adjuvant chemotherapy for LABC (see Table 1) [10-13, 15, 31, 32]. Some studies included patients with smaller tumors. The studies show mixed results and include diverse populations and treatment algorithms.

The study by Mauriac et al. randomized 272 patients with breast cancer tumors larger than 3 cm to either surgery followed by chemotherapy or neo-adjuvant chemotherapy followed by surgery (66%) or radiation therapy (33%) depending on response to neo-adjuvant chemotherapy. At 48 months of follow-up, overall survival was higher in the neo-adjuvant chemotherapy group compared to the surgery group (87% versus

74%) (p=0.04) [11]. Scholl et al. randomized 390 breast cancer patients with tumors greater than 3 cm to either neo-adjuvant chemotherapy

Table 1 – Summary of Selected Randomized Controlled Trials of Neo-Adjuvant Versus Adjuvant Chemotherapy in the Treatment of LABC

Abbreviations:
S - surgery

	AJCC TNM STAGE	TREATMENT	PATIENTS	OVERALL SURVIVAL (%)
Mauriac (1991)	T >3 cm	S → CT CT → S	138 134	74 (4-year) 87 p=0.04
Scholl (1994)	T >3 cm	RT→ S→ CT CT→ RT→ S	190 200	78 (4.5 years) 86 p=0.04
Semiglazov (1994)	IIa - IIIb	CT/RT→S→CT RT→S→CT	137 134	86.1 (5 year) 78.3 ns
Powles(1995) Makris(1998)	IIa - IIIb	S→CT/H CT/H→S→CT/H	107 105	78 (4 year) 78 p=0.98
Fisher (1997)(1998) NSABP-B18	I- II	CT→S→CT S→CT	743 752	79.6 (5 year) 80.0 p=0.83

CT - chemotherapy
RT - radiation therapy
H - hormone therapy
ns - not statistically significant ($p > 0.05$)
T – Tumor Size (cm)
→ - indicates sequential use of various modalities

and radiation therapy or radiation therapy only prior to surgery. With a median 54 months of follow-up, they found that overall survival was increased in the neo-adjuvant chemotherapy group compared to the radiation therapy only group (86% versus 78%) (p=0.039) [13]. Three randomized studies have failed to demonstrate a survival difference for neo-adjuvant chemotherapy. A similar trial to the Scholl et al. study by Semiglazov et al. randomized 271 patients with disease stage IIa to IIIb to neo-adjuvant chemotherapy and radiation therapy or radiation therapy only prior to surgery and adjuvant chemotherapy for both groups. They reported an estimated 5-year overall survival of 86.1% for the neo-adjuvant group versus 78.3 % for the radiation therapy only group (p>0.05) [15]. The study reported by Powles et al. and

the update by Makris et al. randomized 212 breast cancer patients to neo-adjuvant chemotherapy plus tamoxifen therapy followed by surgery and adjuvant chemotherapy versus surgery followed by adjuvant chemotherapy. After a median follow-up of 48 months, there were no differences in overall survival between the two groups (78% versus 78%) (p=0.98) [10]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 [32] study is included in this review because it is the largest and most comprehensive study of neo-adjuvant versus adjuvant chemotherapy to date. It includes breast cancer patients with a disease stage of I or IIa and b, the mean tumor size in the study was 3.5 cm and thus is of only limited comparison to LABC patients. A total of 1495 patients were included in the report, 5-year overall survival was similar for the neo-adjuvant (79.6%) and adjuvant (80.0%) chemotherapy groups (p=0.83) [32]. Although it is difficult to directly compare the randomized studies because of different populations and treatment algorithms, it still remains unclear if neo-adjuvant chemotherapy in patients with LABC will impact 5-year survival.

Many non-randomized, case series of LABC patients treated with neo-adjuvant chemotherapy have been reported in the literature [5, 14, 33-41]. They report 5-year overall survival of 38 to 80%, depending on disease stage or treatments used.

2. Theory of Neo-Adjuvant Chemotherapy

There are practical and biological arguments for the use of neo-adjuvant chemotherapy in the treatment of LABC. Firstly, the response of the primary tumor to the specific chemotherapeutic drugs can be monitored. When the drugs are given prior to tumor removal, the response of the tumor in terms of shrinkage in size can be followed clinically. Some studies suggest that women with tumors that have a good response to chemotherapy have a better prognosis than those with tumors that do not respond [40, 42, 43]. Patients who respond to neo-adjuvant chemotherapy can be continued on a similar regimen after local/regional treatment with the assumption that any residual tumor cells are likely to be sensitive to the previous drugs. If only adjuvant chemotherapy is used, then there is no clinical monitor or method to assess the tumor response to the chemotherapy, and some patients not responsive to the chosen drugs will receive ineffective treatment.

Secondly, drug resistance is minimized by early exposure to systemic therapy. Resistance of cancer cells to chemotherapy is a major cause of treatment failure [44]. Experimental studies have shown that the number of resistant cells increases with tumor size, and the Goldie-Coldman hypothesis [45] suggests that once a tumor is clinically detectable ($1X10^6$ cells or 1 cm in diameter) there is at least one cell line that will be resistant to one chemotherapeutic drug. For LABC, which includes tumors larger than 3 cm, it is likely that a number of cell lines have developed resistance to chemotherapeutic drugs and therefore early exposure theoretically limits the development of any more drug resistant clones. This theory would also support the use of multiple drugs for chemotherapy in order to kill resistant clones with an alternate drug [45, 46]. Thirdly, experimental and animal studies suggest that as any tumor grows, the rate of proliferation of individual cells decreases [44]. Removal of some, but not all tumor cells theoretically shifts the remaining tumor cells into increased proliferation rates [47-49]. In a patient with LABC, surgery could remove the clinical tumor in the breast but there may be microscopic non-detectable tumor cells remaining in the breast, lymph nodes, or at a distant site of spread. Theoretically these remaining tumor cells could shift to increased rates of proliferation. Some animal studies suggest that the use of chemotherapy before surgery can reduce the potential for increased proliferation rates in residual tumor cells [44, 48].

3. Surgery versus Radiotherapy Following Neo-Adjuvant Chemotherapy

When patients are treated with neo-adjuvant chemotherapy a proportion of the patients will experience shrinkage of the primary tumor. The response of the primary tumor can be classified as complete, suggesting that the tumor is now clinically undetectable, or partial, suggesting the tumor is clinically detectable but is smaller in size than prior to treatment. In patients who "respond" to neo-adjuvant chemotherapy, the modality used for treatment of the primary tumor can be either surgery or radiation therapy. Two randomized studies have examined the issue of local treatment of the primary tumor by surgery or by radiation therapy after neo-adjuvant chemotherapy (See Table 2) [50] [51]. An early study by De Lena et al. randomized 132 disease stage III breast cancer patients to receive either surgery or radiation therapy after neo-adjuvant chemotherapy. They reported median survival of

49 months in both groups (p>0.05) [51]. A study reported by Perloff et al. treated 137 disease stage III breast cancer patients with neo-adjuvant chemotherapy, 87 patients were then randomized to receive either surgery or radiation therapy as local treatment. Median survival was 39.0 months for the radiation therapy group and 39.3 months for the surgery group (p=0.96) [50]. Neither study was able to show a significant difference in local recurrence, median disease free survival, or median overall survival for those treated with surgery versus radiation therapy.

Table 2 - Summary of Selected Randomized Controlled Trials of Radiation Therapy versus Surgery After Neo-Adjuvant Chemotherapy in LABC

	AJCC TNM STAGE	TREATMENT	PATIENTS	MEDIAN DFS (MONTHS)	MEDIAN OS (MONTHS)
DeLena (1981)	Stage III	CT→RT→CT CT→S→CT	57 67	22.0 15.0 ns	49.1 ns 49.1
Perloff (1988)	Stage III	CT→RT→CT CT→S→CT	44 43	24.4 29.2 ns	39.0 39.3 ns

Abbreviations:

S - surgery
CT - chemotherapy
RT - radiation therapy
H - hormone therapy
ns - not statistically significant ($p > 0.05$)
DFS - disease free survival
OS - overall survival
→ - indicates sequential use of various modalities

4. Breast conservation considerations

A potential advantage of neo-adjuvant chemotherapy is to allow more LABC patients to be treated with breast conserving local treatments like radiation or segmental mastectomy (i.e. breast conservation surgery). A number of studies have reported tumor response rates for neo-adjuvant chemotherapy [23]. The response rates to neo-adjuvant chemotherapy are classified as:

a. Complete - no detectable tumor
b. Partial - some residual tumor but smaller than before treatment
c. No response - tumor of same or larger size

The response can be measured clinically by physical examination and/or mammography or ultrasound of the breast; or it can be measured pathologically, by measurement of a surgically removed specimen. Clinically complete response proportions range from 5 to 66% with larger studies reporting proportions of 10 to 25% [12, 14, 15, 37-39, 42, 52-55]. Proportions of partial response are as high as 80 to 85% [15, 42, 54, 55]. Pathological response proportions are generally lower than the corresponding clinical proportions. Proportions of pathological complete response range from 1.5 to 29%, with most studies reporting less than 10% [12, 15, 37-39, 42, 52-55]. The greater the clinical and pathological response to neo-adjuvant therapy, the more likely that breast conserving local therapies will be used.

Calais et al. [41] showed that breast conserving therapy could be performed in 49% of patients with tumors greater than 3 cm who were treated with neo-adjuvant chemotherapy. Schwartz et al. [14] was able to perform breast-conserving surgery in 34% of patients treated with neo-adjuvant chemotherapy. When Bonadonna [5] treated patients with tumors greater than 3 cm with neo-adjuvant chemotherapy, he was able to achieve breast conservation in 81% of patients. Two randomized studies [12, 31] showed statistically increased rates of breast conserving surgery in patients treated with neo-adjuvant chemotherapy when compared to patients not treated with neo-adjuvant chemotherapy. The NSABP B-18 study, which included only disease stage I and II, reported that a segmental mastectomy was performed in 67% of the neo-adjuvant chemotherapy group and only 60% of the adjuvant chemotherapy group ($p=0.002$) [31]. This trend was even more dramatic in tumors of increasing size. For tumors greater than 5 cm, the use of segmental mastectomy in the neo-adjuvant group was 22% versus 8% for the adjuvant chemotherapy group ($p=0.008$). The randomized controlled trial by Powles et al. showed an increase in the use of breast conserving therapies for patients treated with neo-adjuvant chemotherapy and tamoxifen (28%) versus those treated with adjuvant chemotherapy and tamoxifen (13%) ($p<0.005$) [12].

E. Introduction to Medical Decision Analysis

Decision-making involves a choice from available alternatives, ideally after consideration of the potential positive and negative consequences of each choice. All investigation and treatment recommendations given to a patient involves an aspect of decision-making on the part of the physician and patient. In some cases the "treatment of choice" is quite clear, but in others it is not. Decision making in health care can be particularly complex, potentially involving diagnostic and therapeutic uncertainties, patient preferences, values and costs [56].

A discussion regarding decision making for a treatment program should first clearly identify the problem of interest [56]. Secondly, we must recognize that there are multiple perspectives of the problem. There is a need to frame the problem in terms of the different perspectives to fully identify all values and objectives related to the problem [56]. This can be accomplished by a general discussion about the stakeholders of the program, their role in the decision-making process, and all relevant values and objectives according to each stakeholder group. The stakeholders in medical decisions can consist of the patient seeking care, the provider of the care (i.e. physician and the institution), the payer of the care (institution, insurance, government, taxpayer/society), and society at large.

The objectives of a program from the patients perspective may be: access to and speed of obtaining care, effectiveness of care (maximizing positive consequences), minimizing negative consequences and maximizing of quality of life both during and after treatment. The objectives of a program from the providers' perspective may be: to maximize positive consequences while minimizing negative consequences for the maximum number of patients. The objectives of a program from the payer's perspective may be: to provide the maximum benefit to the maximum number of patients with the limited resources. The payer is also concerned about the opportunity costs of using the resources for one program which will then not be available for another program. Decisions must be made as to the allocation of scarce resources within the entire health care system over a number of competing programs to maximize the benefit in terms of health of the population. The objectives of a program from the perspective of society may be: to satisfy an underlying altruistic

need, and also to provide the maximum benefit to society (productivity, growth, development and happiness), as they must account for the opportunity costs of the program within the whole society.

Decision analysis is the application of quantitative methods and modeling to analyze decisions under uncertain conditions [57]. Decision analysis is a proactive approach to decision-making in which both evidence and values can be integrated into a single framework [56]. Decision analysis is a method for structuring and modelling a decision process which can organize complexity, represent and account for uncertainty, and provide a framework to deal with multiple outcomes [58]. Decision analysis is not intended to provide an "answer", but instead its goal is to allow the decision maker to have a better conceptual understanding of the whole problem and provide insight into the alternatives and outcomes. It does not solve the problem, but provides another important tool to help guide a decision process. Quality medical care is determined by two factors; the quality of decisions, and the quality of the execution of those decisions [56]. If the quality of the decision process is limited then it does not matter how skilful the execution, as quality medical care will suffer.

Following is a general discussion of decision theory and analysis; the specifics of the present analysis are discussed in section VIII.

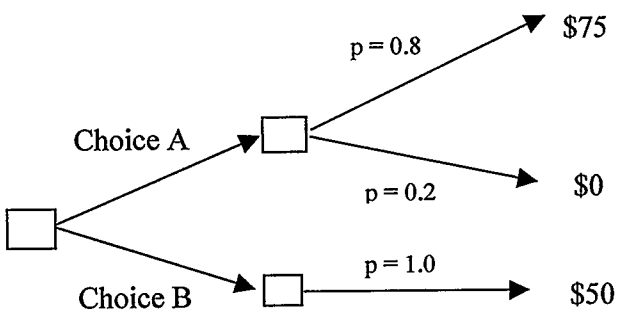
1. Background theory of decision analysis methods:

Decision analysis methodologies and underlying theory have evolved from the business and industry sectors. The basis of most decision analysis techniques is expected utility theory that was first described by von Neumann and Morgenstern in 1947 [58, 59]. The theory states that given certain assumptions and conditions, people should make choices (decisions) that maximize the expected utility. The expected utility of a choice or alternative is the additive total of the expected value for each possible outcome of the alternative. The expected value of any single outcome is the product of the utility value and the probability of the outcome. The utility value consists of the value units that can be applied to an outcome to represent the desirability of that outcome to the decision maker. The calculation of expected utility

requires the probability of the event occurring be known, and that a utility value for the outcome be assigned.

As an example, consider a choice between receiving 50 dollars for certain versus a gamble where the probability of winning 75 dollars is 80% and the probability of winning no money is 20%. This can be represented diagrammatically as seen in Figure 2. If we multiply the probability of 0.8 by the utility of 75 dollars we get 60 dollars for an expected value for that outcome; an expected value of 0 dollars is obtained by the same method for the other possible outcome of choice A. The two expected values can be added together to arrive at the expected value of choice A, which would be 60 dollars (60 + 0 dollars). The expected value of choice B is the probability (100%) times the utility value of 50 dollars, which gives an expected utility of 50 dollars for choice B. This calculation method for determining expected value can be viewed as equivalent to presenting the decision problem to many people and averaging the total dollars received by the number of people. So, although any single individual could receive 0, 50 or 75 dollars a choice must be made without knowing the actual outcome (i.e. choice is made under uncertainty), the average of those who choose alternative A is 60 dollars and those who choose alternative B is 50 dollars. According to expected utility theory, given the choice a person should choose alternative A because the expected utility is higher (maximized). This simple example can be carried to a more complex decision situation and not involving money as the utility value, and thus provides a basis for decision analysis methodologies.

Figure 2 - Diagrammatic form of a simple decision between two alternatives for calculation of expected value of each alternative



There are a number of general conditions and assumptions regarding a decision maker's behaviour that needs to be met in order to use expected utility as the basis for decision analysis [58].

a. Ordering and transitivity
   - a decision maker can order (establish preferences) alternatives, and if A>B and B>C then A>C.

b. Reduction of compound uncertain events
   - a decision maker is indifferent (no preference) between a compound uncertain event (complicated set of gambles) and a simple uncertain event (single gamble) that is a reduced form of the compound uncertain event.

c. Continuity
   - a decision maker is indifferent between some level of outcome (A) and a gamble (A1 versus A2) given that the outcomes of the gamble are above and below the level of (A) (i.e. A1>A>A2).

d. Substitutability
   - a decision maker is indifferent between a certain event and an uncertain event with the same expected value (opposite to b).

e. Monotonicity
   - given two gambles with the same outcomes, a decision maker will prefer the gamble with the higher probability of winning the preferred outcome.

f. Invariance
   - all that is needed to determine a decision makers preferences among uncertain events are the probabilities of events occurring and utility values for each outcome.

g. Finiteness
   - no outcomes are considered infinitely bad or good.

It is agreed that under most circumstances these assumptions and conditions hold, but controversy exists regarding some of the assumptions [58]. In general, if the decision-maker agrees with the assumptions then it is possible to find a utility

function to evaluate the outcome, and the decision maker should make choices based on maximizing expected utility.

2. Clinical Problem

The choice of an appropriate clinical problem is the first step in the development of a useful decision analysis. A clinical problem amenable to decision analysis should be one in which there is no clear consensus regarding the "best treatment". There should be a number of alternatives to choose from, and the literature and experience should not suggest a dominant alternative. An alternative to providing a decision analysis would be to perform a clinical trial which can test similar hypothesis and objectives. Some of the advantages of using a decision analysis for treatment of LABC are that it is relatively inexpensive, no long term follow-up is required (up to 10 years or more for a clinical trial), unpleasant or dangerous therapies or outcomes can be modelled, and it can identify areas in which a clinical trial may be of benefit to provide more information.

3. Target Population

In order to develop an appropriate model for decision analysis, identification and description of the target audience at the outset is imperative. The steps in the model, important outcomes and values will be specific to different audiences, even for the same clinical problem. Potential audiences could range from patients, to doctors, to other healthcare workers, to policy makers, or to society. The objectives of each group may differ for a single clinical problem. In our case (treatment options for LABC) patients may be only interested in treatments with the greatest potential for cure, the fewest side effects, and/or highest quality of life. Doctors may be interested in treatments that cure the most patients; and policy makers may be interested in treatments that are the most cost-effective (i.e. cost per life year saved). It is therefore very important to define the target audience for the decision analysis at the outset. The clinical problem, along with the chosen stakeholders, becomes the decision context for the problem.

4. Values and Objectives

Once a decision context has been identified there are two ways to approach it. Alternative-based thinking suggests that the next step in the decision process should be the identification of alternatives, then selecting the "best" alternative from the group of alternatives. Unfortunately, "best" is typically not precisely defined in terms of decision objectives that relate to the decision maker's values, and this method may be constraining in terms of creative solutions. Keeney [60] suggests that the next step should be to identify the values that one is trying to impact in the decision process, which he terms value-focused thinking. Keeney argues that values are more fundamental to the decision process than alternatives because the reason one is interested in a decision at all is because it impacts our values.

All decisions involve a trade-off between some values for the decision maker. Values can be defined as the things that matter, or are important to a decision maker (e.g. life, health, freedom, happiness). The abstract notions that are values can be made more explicit by describing objectives. The objectives qualitatively state all that is of concern in the decision context; they provide guidance for alternatives and are the foundation for any quantitative modeling of the problem [60]. The objectives are the statements of what one wants to achieve. There are two types of objectives, means objectives and fundamental objectives. Both types of objectives have three features: a decision context, an object, and a direction of preference [60]. A means objective is an objective of interest because of its implication for the achievement of another more fundamental objective; it is the means to a fundamental objective. A fundamental objective is an objective which has intrinsic value to the decision maker and is an essential reason for interest in the problem. For example, a means objective in breast cancer treatment might be to minimize nausea and vomiting associated with chemotherapy. This means objective is related to the fundamental objective of maximizing quality of life. This fundamental objective can be described in terms of many means objectives; nausea and vomiting, pain, sleep, and another important aspects of quality of life.

Once a list of objectives has been generated for the decision problem the fundamental objectives need to be identified. A fundamental objective is an essential reason for

interest in the decision problem and refers back to the values [60]. Fundamental objectives can be identified by asking the question " why is this important?". A fundamental objective has intrinsic value to a person (e.g. length of life, happiness). After the fundamental and means objectives are identified, the list of possible alternatives that will potentially influence the objectives should be considered for the decision problem. It is the identification of the values and objectives that guides the development of alternatives in value-focused thinking [60].

The fundamental objectives are also used to identify the measure of success of the various alternatives. For example, if one of the fundamental objectives is happiness, then the outcome of each alternative needs to be measured in terms of its impact on happiness. The process of identifying a measure for the objectives is the process of identifying attributes. An attribute can be thought of as the scale upon which one will measure the achievement of an objective. A utility is a mathematical description of a decision makers preferences for the various measures of an attribute. They are the constructed preference weightings attached to the outcomes.

Outcome measures can range from only two possibilities of a single attribute, to multiple possible outcomes of a single attribute, to multiple possible outcomes of multiple attributes [56]. An attribute is a single domain or characteristic along which one is to measure an outcome. The simplest outcome is a dichotomous variable of a single attribute; if the attribute is survival the two outcomes could be alive or dead. An example of a single attribute which describes a continuous outcome is survival time, where the outcome is measured along a continuous scale (e.g. time) and can take on any value of that scale (multiple possible outcomes), but is still only measuring a single characteristic. The most complex outcomes are those in which more than one attribute or characteristic is measured; and there are multiple possible outcomes for each characteristic[56]. An example would be breast cancer treatment, which could be measured in terms of survival and quality of life. Each of these attributes or characteristics could have multiple possible outcomes, survival can be any value along a time scale and quality of life could also be measured along a scale from a value of 0 to 1 (0=death and 1=perfect health).

Analysis of decision problems that incorporate multiple attributes requires that one must account for trade-offs between the attributes to determine the best alternative[56]. One way to evaluate the trade-off in values between the attributes is to convert the measurements to a single scale that reflects the values associated with each attribute[56]. For the example above of breast cancer treatment, the outcomes could be measured on a single scale, quality-adjusted survival, which would incorporate both survival time and quality of life. If one produces a graph of quality of life values versus survival time, the area under the curve will be a function of both the quality of life and the survival time measured on a single scale[56]. For every unit of survival time, time can be multiplied by the quality weighting for that period (quality of life value), then this value for all time periods can be added together to produce a value for the total quality adjusted survival for that patient. The total quality adjusted survival time can then be compared for the different alternatives in the decision process; the alternative that yields the largest quality adjusted survival time should be the preferred alternative. The use of quality adjusted survival in this way is only valid if the ratio nature of the measure is true, i.e. that one year at quality 0.5 must be equivalent to 6 months at quality 1.0 [56]. For this to be true, the quality measure must be a global measure of the state of health, and not just disease specific; the ratio scale of the quality measure must be valid, so that a measure of 0.5 is exactly half as desirable as 1.0; and the use of time should represent the subjects preference for the quality of life in a given health state [58].

A scale of preferences, or utilities, for the various possible measures of the outcome is then constructed. A utility can be defined as the quantitative measure of the strength of a person's preference for an outcome [56]. Most often the utility for an outcome is represented by a numerical value representing the decision maker's preference, so that higher values are more preferred than lower ones. The development of a good utility scale for the selected outcomes is key in decision analysis based on expected value (utility) theory. In health care, a utility can reflect how a person values a certain state of health. The valuation of health states is the basis for the development of quality of life measures. In decision analysis, it is not the measurement of "quality of life" per se that is important, but the development of a utility scale (preference ranking) for the potential health states [56]. There are a number of methods described to calculate the

utilities of health states; the standard gamble technique, the time-trade-off technique, willingness to pay, and health indexes. There are also a number of references which provide utilities derived from previous work [56, 61-64].

The use of quality-adjusted survival as a utility depends on three criteria [56]:

1. the utilities must reflect preferences under uncertainty
2. there must be constant proportional trade-off. Which means that the time one is willing to give up in order to improve health is independent of the length of life (i.e. no time preference).
3. there must be risk neutrality

However, it has been shown that if the last two criteria are met approximately then it may adequately represent the utility. Also, an adjustment can be made for time preference by using discounting of health years.

An outcome measure which can be used in decision analysis is that of quality adjusted life years (QALY). This is an outcome that primarily measures the duration of life expectancy, with the addition of a quality weighting to reflect a loss of the quality of life based on different health states [58]. It appears to be more informative because of the incorporation of the quality measure. A quality value is assigned to each possible health state based on its desirability by subjects. The number of years, or other appropriate time duration, is multiplied by the quality rating for that health state to yield a value of quality adjusted life years. This can be interpreted as the corresponding reduced number of years of life in perfect health which would be valued in a similar manner to the full number of years in some heath or ill-health state.

One of the assumptions that must be satisfied when using the QALY as an outcome is that of utility independence [65]. The outcome of QALY is a combined outcome measure taking into account length of life and quality of life. This assumption means that the utility placed on length of life is independent of the utility placed on quality of life. The second assumption that must be met is "proportional trade-off", one must be willing to give up a portion of one's life years to improve one's quality of life and that

the proportion of life one is willing to give up is independent of the total length at the outset [56].

5. Risk Attitudes

A risk attitude is a fundamental characteristic of a decision maker; it reflects the person's attitude regarding the element of risk in uncertain conditions. For example, say a person is faced with a decision between a gamble with possible outcomes of 100 dollars or 0 dollars versus an amount that is available for certain. Expected value theory suggests that the person will choose the alternative that maximizes the expected value (probability of the event times the utility (value)). For a person who is "risk neutral", they would be willing to accept, for certain, the amount equal to the expected value from the gamble (which will be dependent on the probabilities). For a person who is "risk averse", they would settle for a certain amount less than the expected value of the gamble because they would rather have the certainty of having money in hand than "take the chance" of losing it all with the gamble. The opposite is true of a "risk seeking" person; they would accept a certain amount that is higher than the expected value of the gamble because they want to take the risk for the big pay-off of the gamble. This risk attitude characteristic is situation dependent, so that the same person will not have the same risk attitude in all decision situations, in some they may be risk averse, in some may be risk neutral, and in some may be risk seeking. If the utilities are derived using the standard gamble technique then they will also reflect the risk attitude of the person [56].

6. Time Preference

The concept of a time preference suggests that the value placed on an objective in the future is less than the value for the same objective at the present time [56]. If a decision maker has a time preference than the utility placed on a health state is dependent not only on the nature of the health state but also on when and how long the state is endured. For example, one might be willing to give up more "healthy" years in exchange for some period in a health state if it occurs 10 or 20 years in the future compared to if it was to occur in the next 5 years. One way to account for the issue of time preference is to apply discounting for future health outcomes. Discounting refers to the application of a mathematical formula to the outcome value

which will reduce the value based on the number of years from the start that the outcome occurs [56]. This concept is similar to the arguments for discounting in economics of future costs. There are arguments for and against the use of discounting health outcomes [56]. Both costs and health outcomes should be discounted, and they should be discounted at the same rate. The value of the discounting rate should be determined by the real rate of return on long-term government bonds (about 3%) but should also be consistent with rates used in other similar published studies and a range for sensitivity analysis chosen of about 0 to 7% [56].

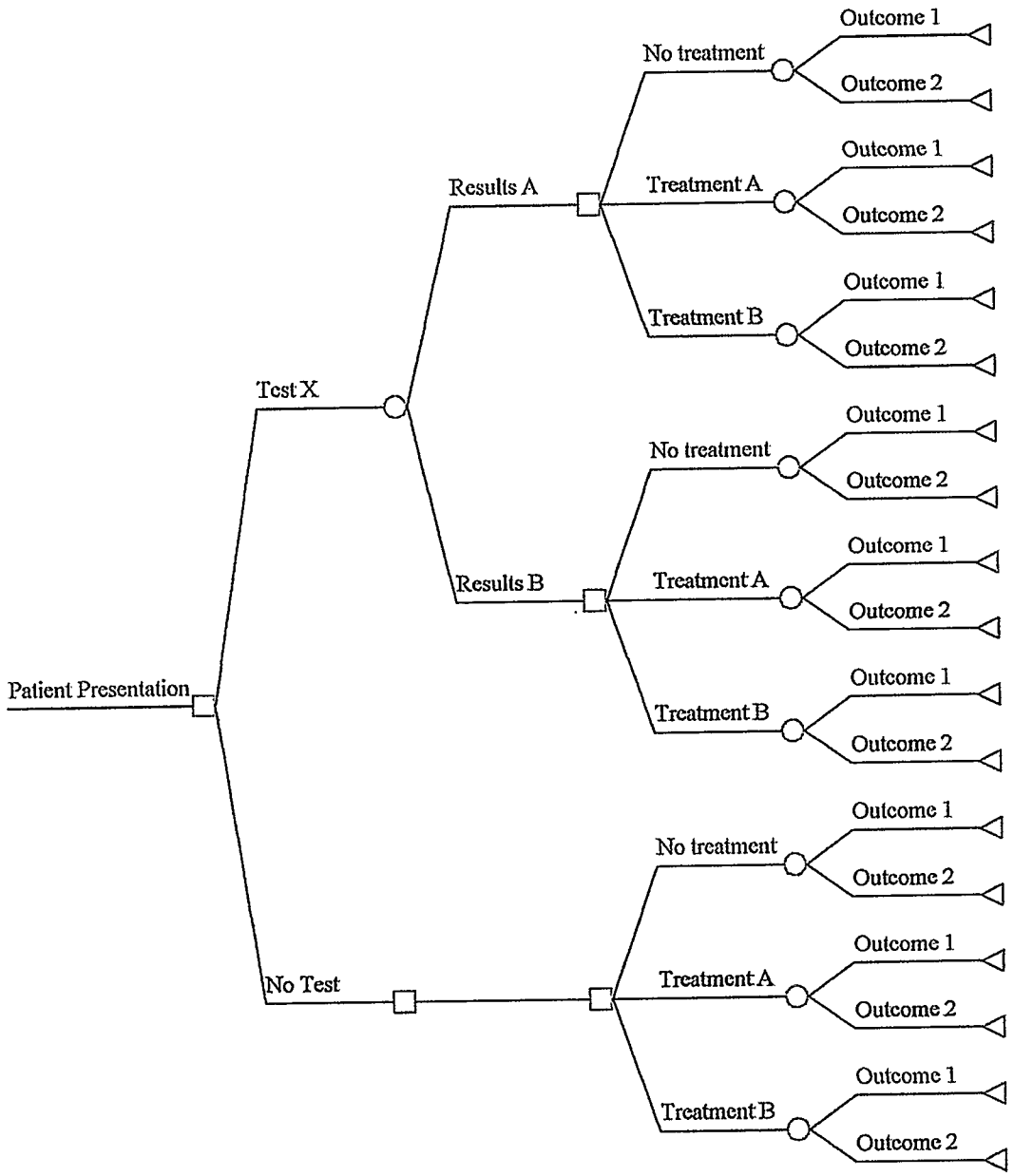
7. Alternatives

The next step in the formation of the decision analysis framework is to define and include the alternatives to be considered. This step relies on an understanding of the disease and treatment process. All clinically appropriate treatment alternatives should be described and included in the model. The various treatment alternatives considered will be described along with the model structure.

8. Model Structure

The next step is the development of a model or structure that describes the clinical problem in a representative way. Almost all medical decision analyses are modeled using a "tree" structure [66]. A generalized clinical decision tree is shown in Figure 3. The tree structure, by convention, begins with the clinical starting point on the left; the tree is then diagrammed from the left to right with the branches representing the points of decision or outcome. The tree is modeled in a logical order and follows the temporal sequence that the real clinical steps would occur [65]. Points in the process were a decision has to be made are represented as decision nodes or choice nodes (small square). This is a branch point in the tree structure with each branch representing one of the possible alternative choices. Points in the process where an outcome/outcomes are expected (i.e. test results, results of treatments etc.) are represented by chance nodes, these chance nodes are branching points in the tree structure with each branch representing each possible outcome from the proceeding activity/actions. The ultimate outcome of interest in the clinical problem is diagrammed at the far right side of the tree structure following all decision and chance nodes.

Figure 3 - General Decision Tree Structure



Adapted From Weinstein et al, 1980 [84]
Data 3.5, TreeAge Software Inc.

9. Time and its incorporation into the model

The issue of time frame is important in clinical decision analysis. It depends mostly on the nature of the clinical problem at hand, and the intended use or objective of the analysis. For some clinical problems this may mean a short time frame (e.g. immediate complications of a treatment), for clinical problems which are looking at chronic illness or treatment outcomes such as survival, the time frame will need to be much longer (e.g. survival after treatment for a cancer). In choosing a time frame appropriate to the situation, one faces a trade off between accuracy and parsimoniousness [65]. For short time frames one can be more complete, for longer time frames a simpler decision tree may be more appropriate to model the clinical problem.

Another issue with regard to time and modelling is in clinical situations where the time horizon of the problem is long or indeterminate [65]. When the time horizon for a problem is long, there is likely to be fluctuation of probabilities over time. For example, if we were looking at the recurrence of a disease after some finite treatment, the probability of recurrence may decrease with time since treatment. This "changing" probability is difficult to model in a "classic" decision tree with a fixed time horizon or time frame of follow-up. Another issue with fixed time frames is the issue of health discounting [65]. One unit of health today is valued more than the same unit of health in the future. There is a natural element of discounting of health. This discounting effect will be important in the calculating of utility values in the decision analysis. If the clinical problem has a short time horizon than any loss of health outcome with treatment will be realized early and no discounting will be present. But if the time horizon is longer, people are less concerned about complications (or loss of health) that may occur in the future as opposed to ones that may occur in the present [57]. A clinical problem may be interested in looking at events that occur over a lifetime, the conventional decision tree defines a finite length of time frame for all participants. Thus it is very difficult to calculate probabilities and utilities for a decision tree over a "lifespan" time frame, which will vary from person to person.

The use of a Markov process for modelling outcomes can overcome many of these issues faced by the conventional decision tree over long follow-up periods [57]. Conceptually, the standard or conventional tree shows how a group of patients will move from an initial health state to a number of various health states over a fixed period of time with fixed probabilities and utilities associated with movement to the end states. The Markov process allows us to model the transition of a group of patients from an initial health state/s to a number of health states in a more dynamic way. It uses "short" (situation dependent) time cycles to describe transitions between health states with a set of probabilities and utilities attached. It will then repeat the "cycle" of transitions beginning at the end of the last cycle and will allow one to change the probability of transition between states or utility of health states at the end of each cycle. An infinite number of cycles can be run to simulate transitions over long periods of time. The Markov modelling process usually incorporates an absorbing health state; this is a health state that one cannot move out of (e.g. Death). The Markov process can thus be run the number of cycles to move all persons into the absorbing state. This can mimic the natural process of following a cohort through a lifespan with changes in probability and utility over time as required.

The first step in the development of a Markov process is to define a set of health states [57]. These health states should represent, in a basic way, the reality of the clinical situation. The health states should be mutually exclusive of each other so that a single patient can exist in only one health state at one time [57]. The next step is to define the length of a cycle; this will depend entirely on the clinical context and goal of the analysis. The length of a cycle can be short (days, weeks, months) for short-term outcomes of interest or they may be longer in duration (months, years) for long-term outcomes. The next step is to describe the ways in which a patient can transition between the various health states during any one cycle. A flow diagram, which can represent all possible movement from one health state to the others, is the most intuitive [57].

The Markov process is analyzed by first defining the proportions of the cohort which enter the process in each health state. During the first cycle, patients are allowed to move between the health states according to the defined probabilities for that cycle.

At the end of the cycle, all transitions will have taken place and a new distribution of patients will exist in each health state. The utility value assigned for each health state is then multiplied by the proportion of patients in the group. The utility values calculated for all groups (i.e. health states) are added up to provide an overall quality-adjusted cycle value which represents the total contribution of that cycle to "quality health time" for the cohort. This process is then repeated and the calculated utility values are added up for all the cycles to yield a total value. Because all terminal branches of the decision tree can have the same Markov process at the end, the process will yield different total value results for each different branch by virtue of a different distribution of patients starting in the different health states, and different values for the transition probabilities depending on which treatment branch is used. This will allow one to directly compare the different decision tree pathways because each one will be associated with a calculated total value. The higher values for the total value should represent the preferred clinical strategies.

10. Estimating Probabilities and Utilities

Within the decision tree the two basic elements (apart from the tree structure) are the probabilities and the utility values for each outcome or Markov state. A probability is a quantitative estimate of the likelihood of an event in the decision tree will occur. An outcome utility value is a quantitative expression of the desirability of such an outcome happening [67]. Probability-weighted utilities are then used for expected-value calculations in the tree.

The usefulness of a decision analysis will rely on the accurate estimation of these values. The probabilities should be derived from the most accurate information source available. Sometimes the most accurate information may come from the published literature, other times the most accurate information may be derived from studies or data on the population under consideration (data which most closely fits the population under consideration). Within the published literature, there is a generally recognized hierarchy to the quality of information [56]. The highest quality literature is a meta-analysis, then systematic literature reviews, then published randomized controlled trials, then other published studies (uncontrolled trials, case series, case reports). A computerized search of literature databases (e.g. Embase, Medline)

should be used to identify relevant articles, which can then be critically reviewed and information subjected to the hierarchy described. The highest quality studies should be used to derive the estimate of the probability. It is possible that a probability estimate cannot be derived from the published literature; possible alternative sources of information are an existing database, personal data collection, expert opinion, personal experience, or best guess.

Depending on the type of data that is available, there is likely to be some aspect of uncertainty to the estimate of probability. For topics in which there are good quality studies, this uncertainty may be small; for topics in which the estimate is based on poor quality literature this uncertainty may be larger. Because there is uncertainty in the estimate one should always provide a "reasonable" range for the value of the probability. The range of values can come from 95% confidence intervals in published studies or from a high-low range of values specified in different studies. The importance of defining the uncertainty around the estimate is related to the sensitivity analysis and testing of assumptions of the model.

Rates for outcomes under consideration that are synthesized from the medical literature can be converted to transition probabilities for the Markov model according to accepted methods. The formula

$$P(t)=1-e^{-rt}$$

can be used, where P(t) is the probability of an event during the cycle time, r is the rate, and t is the duration of the cycle expressed in the same units as the rate. [56, 68] The estimation of the outcome value will depend on the type of objectives and thus outcomes defined by the analysis. For simple outcomes such as alive/dead, disease/none or complication/none the outcome value may be the number or proportion of individuals with/without the desired outcome. Some analyses will have more than two outcomes; this usually means that an outcome value is placed on each outcome based on a preference or desirability for the outcome. Because all outcome values are a measurement of a subjective process and the tools of measurement of these subjective values are inaccurate the uncertainty associated with the outcome values is relatively large. Again the range of plausible values should be defined with in the analysis for use in a sensitivity analysis. There are now a number of databases

that have gathered information from studies on the outcome values in a variety of health states and diseases, which can be informative in this process [61].

11. Sensitivity Analysis

Sensitivity analysis refers to the testing of the assumptions of the decision model. With the identification of the decision problem, underlying values leading to description of the fundamental objectives, listing of the outcomes and alternatives, and identification of the associated probabilities and utilities the model is ready to be used to determine the preferred alternative. Before a chosen alternative is identified we need to account for two factors, variability and uncertainty. Variability refers to the heterogeneity among individuals of a population with regard to factors that may affect the alternatives [56] such as age, sex, previous medical history, risk factors, prognostic factors, and response to treatments. The use of decision trees or Markov models allows for the analysis of a cohort of similar individuals, but we know that all individuals will not react and respond in the some way. We need to be able to model the variability in important factors within the population for which the analysis is tailored, as this variability may result in different alternatives being identified as preferred.

The variability among individuals of a population for a particular characteristic can be modeled by using separate inception cohorts for the decision model that vary according to the important factors. Another method to model variability is to use a Monte Carlo simulation technique with a Markov model. Individuals with certain characteristics can be "followed" through the decision model with the use of tracker variables [56]. These tracker variables will determine the next set of probabilities and utilities to be used in the analysis.

Although the decision model incorporates uncertainty in the outcome of treatment as modeled with probability nodes, there is also uncertainty associated with the actual values used for the model parameters of probability and utility. This parameter (value) uncertainty is due to the error in measurement of the value based on the assumption that they are derived from a measured sample and heterogeneity of the sources (studies) used [56]. For each probability value and utility value in the model,

an estimate of the uncertainty of the value can be given be providing a range of plausible values for the estimate. This range of values can be derived from 95% confidence intervals associated with the estimate from a study, or can be the range of values from different studies. A deterministic approach to sensitivity analysis allows one to "test" the robustness of the interpretation of the analysis when varying the assumptions of the model over the range of uncertainty. Because the true value for the estimate could be any value in the range, the model should be tested over all possible "true" values in order to obtain the correct interpretation of the true state of the problem [69]. The decision analysis is conducted multiple times using the different values for the estimates of probability and utility and the results are compared over the ranges. Sensitivity analysis begins with one-way testing in which only one variable for a probability or utility is varied across the entire range of values [69]. Conducting the analysis with the changing value will result in an expected value for two or more alternative strategies that are equal. This is referred to as the threshold value, equal expected value for two or more strategies. If this threshold value for the variable is within the range of plausible values (range of uncertainty) then the analysis can be said to be sensitive to that variable. This analysis is repeated for all the variables of probability and utility in the analysis to yield a list of "sensitive" variables on one-way analysis. The next step in the deterministic sensitivity analysis is to run a similar group of analysis while changing the values for two variables (two-way analysis) at a time, then three variables at a time (three-way analysis) [69]. The group of variables that are used in the two and three-way sensitivity analysis are usually the variables which were sensitive in the one-way analysis. A final step in then deterministic sensitivity analysis is to perform the analysis using the most extreme conditions, the "best case" and "worst case" scenarios[69]. The end result of the sensitivity analysis should be the identification of a variable or group of variables for which the current model is sensitive to the range of uncertainty. This deterministic method of sensitivity analysis for uncertainty associated with model probabilities and utilities is limited by computational complexity when there are many uncertain variables.

Another method for analysis of parameter uncertainty utilizes a probabilistic approach with Monte Carlo simulations[56]. The uncertainty associated with each variable is

itself modeled as a probability distribution, so that each parameter is not a value but is a distribution of values each with a probability. Similar to an *n*-way sensitivity analysis, the model is run *n* times, each time using a value for each variable chosen from its probability distribution. Because the model is run *n* times, there are n different expected values. All calculated expected values together produce a distribution for the expected outcome, which can then be used to measure the uncertainty associated with the uncertain nature of the parameters of the model.

12. Published Literature

A Medline search from 1966 to present provided a total of 67 published articles which use decision analysis methodology in the area of breast cancer. The Medline search terms used are outlined in Table 3, MESH terms and text words in category 1 were combined with each of the MESH terms or text words in category 2. The titles of journal articles returned from this search methodology were reviewed and all relevant papers were further assessed by a review of their published abstracts. All original studies which include the use of a decision analysis methodology are included to total 67 published studies. No studies were identified that use decision analysis methodology in the area of treatment of LABC. (see Appendix B for reference list)

Table 3 - Summary of Medline search terms used for decision analysis literature selection

Category 1 Mesh terms or text words	*Category 2 Mesh terms or text words*
Breast neoplasm	Markov chains
Breast cancer	Markov model
Breast disease	Markov
Locally advanced breast cancer	Decision support techniques
	Decision model
	Decision analysis
	Cost-benefit analysis
	Cost-effectiveness
	Cost-utility
	Monte-Carlo
	Statistical model

IV. Methods

There are two components to this research project, the survival analysis and the development of a decision analysis framework to address treatment strategies in LABC. Each component will be described separately as follows.

A. Survival Analysis

The study design used for this portion of the project is a population-based retrospective cohort utilizing survival analysis methodology. A standard measure of "success" in the treatment of cancer is the proportion of patients with the disease who survive to a certain time point from the time of diagnosis. Because survival (length of life) is a fundamental objective with intrinsic value for the patient, it can be used to compare the "relative benefit" of different treatments for patients with LABC. Survival analysis is a group of statistical methods which utilize time-to-event data to describe when and how many patients will have the occurrence of a defined endpoint. Time is measured from a defined starting point (e.g. diagnosis, treatment start, or other defined point in the disease process) before the occurrence of the endpoint.

There are two data sources that were used for the survival analysis, the Alberta Cancer Registry and the Screening Project Data 1994-1996. The Alberta Cancer Registry (ACR) is maintained within the Alberta Cancer Board's (ACB) Division of Epidemiology, Prevention and Screening. The ACR collects data on all new primary cancers and cancer deaths occurring in residents of the province of Alberta. It was established in 1942 and began collecting population based data in 1950. New cancers are identified through a number of sources. All pathology reports in which a diagnosis of cancer is made are available to the ACR. Other sources of data are from operative reports, discharge summaries and x-ray reports. Registry personnel then record information about the new case. Coding of information is based on the International Classification of Diseases for Oncology, second edition (ICOD –2) and the Surveillance, Epidemiology and End Results Program of the National Cancer Institute (SEER). The ACR files are matched to Alberta Vital Statistics data for every death occurring in Alberta, data recorded include the date and cause of death. Ad-hoc notification from family, physicians or obituaries may also be recorded in the ACR as

a death. The ACR files are also linked to the Alberta Health registration file to provide vital and residency status of cancer cases. The Screening Project Data 1994-1996 is a database from an ACB project that involved a systematic review of records, for the years 1994-1996, by trained health record personnel to accurately stage breast cancer patients. The project was initiated by the ACB as part of a study of mammography because adequate staging data was not available in the ACR.

Data from the ACR and the Screening Project Data 1994-1996 for the period January 1, 1994 to December 31, 1996 was compiled by ACR personnel for all patients with breast cancer. ACR personnel then stripped all identifying information from the records. A unique identifying number was created for each corresponding entry in both data files. The two data files were provided to the primary researcher, and merged to form the study data file upon which the analyses presented in this project are based.

The population under study is all women diagnosed with invasive adenocarcinoma of the breast in the years January 1, 1994 to December 31, 1996 who fit the criteria for LABC and who were residing in the province of Alberta at the time of diagnosis. LABC is defined as a primary adenocarcinoma of the breast with a primary tumor greater than 3 cm in greatest dimension and/or fixed or matted axillary lymphadenopathy (AJCC Breast Cancer N Stage=N2 or N3), in the absence of metastatic disease (AJCC Breast Cancer M Stage=M0). The time period chosen reflects the need to obtain at least 5 years of follow-up for all subjects and also corresponds to accurate staging data available from the Alberta Cancer Board (ACB). Patients were excluded from the study if they met any of the following criteria:

a. Previous diagnosis of invasive breast cancer (adenocarcinoma)
b. Current or previous diagnosis of breast cancer of non-adenocarcinoma histology (lymphoma or sarcoma)
c. Previous diagnosis of invasive cancer of histology other than non-malignant skin cancer
d. Inability to obtain or missing ACB data

The purpose of excluding patients with a previous diagnosis of cancer is that treatments (radiation or chemotherapy) received for the "other" cancer(s) may potentially impact the treatment and survival associated with the diagnosis of LABC. Non-melanoma skin cancer is not excluded because this type of cancer is not treated with radiation or chemotherapy.

The outcomes of interest in the survival analysis are the overall survival and breast cancer specific survival. Overall mortality refers to deaths within the study population that are attributable to all causes of death, all-cause mortality. Breast cancer specific mortality refers to deaths within the study population that are directly attributable to breast cancer. All deaths in the study population are coded according to the International Classification of Disease, 9th Revision (ICD–9) developed by the World Health Organization (WHO). All patients with a cause of death coded as 174.0 to 174.9, excluding 174.7 (not used in ICD-9), are considered breast cancer specific causes of death. ICD-9 codes which include causes of death as secondary or metastatic disease to distant body sites from the breast would also be considered as a breast cancer specific death; this would include codes 196.0 to 196.9 (lymph nodes), 197.7 (liver), 198.3 (brain), 198.5 (bone), 197.0 (lung), 199.0 (disseminated), 199.1 (other). None of the LABC study patients had a death coded from the list of secondary or metastatic sites. All other causes of death, those not listed above, were considered as causes attributable to overall mortality.

The study variable of particular interest is the chronological order of the various treatment modalities used. Data was available for each patient regarding the type and date for treatments used. Individual treatment modalities are defined as follows:

A. Surgery – Use of either a total mastectomy (removal of the entire breast complex and axillary lymph nodes) or segmental mastectomy (removal of the tumor, a portion of breast tissue around the tumor, and axillary lymph nodes). When a segmental mastectomy is performed, it is followed by radiation therapy on the same side as the remaining breast tissue. When the term segmental mastectomy is used as a treatment option it will be assumed that radiation therapy was always used post-operatively.

B. Chemotherapy – Use of drug(s) administered to the patient for the purpose of killing tumor cells. Drug(s) are given either orally or intravenously and are delivered throughout the body (systemic chemotherapy).

C. Radiation therapy – Use of a radioactive source, external to the patient, directed towards a specific target area for the purpose of killing tumor cells.

D. Hormone therapy – Use of a drug(s) which alters the effect of estrogen on tumor cells. The drugs that are coded in the ACR as hormone therapy include the following: Anastozole (Arimidex), Letrozole (Femara), Megestrol Acetate (Megace), Tamoxifen Citrate (Nolvadex). Surgical removal of the ovaries (oophorectomy) is also coded as hormonal therapy. Hormone therapies work by reducing estrogens effects on the tumor cell through either selective modulation of estrogen receptors (Nolvadex), reduction in production of estrogen (Arimidex, Femara and oophorectomy), or inhibition of estrogen effects (e.g. Megace). A note should be made that Arimidex and Femara were not on formulary with the Alberta Cancer Board until 2001, so their use would have been limited, if at all, in our study population.

E. Transplant therapy – Use of high dose (higher doses than normal) systemic chemotherapy and stem cell (progenitor blood cells in bone marrow) transplant (intravenous infusion of patient's own stem cells to re-populate the bone marrow).

Each record was reviewed and the chronological order of treatments used was established. This review process identified a total of ten different treatment strategies. The sequential nature of individual treatment modalities for each strategy is an important consideration for the ten strategies identified.

Table 4 - Identified Treatment Strategies for Patients with LABC

	TREATMENT STRATEGY
1	S → +/- H
2	S → CT → +/- H
3	CT → +/- H
4	CT → RT → +/- H
5	CT → S → +/- RT → +/- H
6	S → T
7	T → S
8	RT Only
9	H Only
10	None

Abbreviations:

S - surgery
CT - chemotherapy
RT - radiation therapy
H - hormone therapy
T – transplant therapy

These ten strategies can then be further classified as:

1. Standard therapy - surgery followed by any of the other treatments (strategy 1 or 2 above).
2. Neo-adjuvant chemotherapy (chemotherapy followed by any of the other treatments (strategy 3, 4 or 5 above)
3. Other (any other strategy (strategy 6, 7, 8, 9, or 10).

Data received from the ACR includes demographics (date of birth, gender, Alberta residency), date of diagnosis, date of death, ICD-9 coded cause of death, type of treatment and treatment dates. Data extracted from the Staging Project Data included clinical, pathologic and overall stage of disease, clinical and pathologic size of tumor, histologic grade of tumor, number of lymph nodes removed and number lymph nodes with tumor (positive nodes). Below is a list of the variables extracted from the raw data for use in the study.

1. Age at diagnosis – in years
2. Survival from diagnosis – in years, calculated as the time from diagnosis to death or last known follow-up
3. Death (all) – event record of a death occurring from any cause (0 or 1)
4. Death (breast cancer) – event record of a death occurring from a breast cancer specific cause (0 or 1)
5. Disease Stage – AJCC TNM disease stage (2A, 2B, 3A or 3B), represents overall stage (clinical and/or pathological) as judged by trained health record technician
6. Histologic Grade – microscopically determined grade of the tumor (1, 2 or 3)
7. Tumor Size – in centimetres (cm), maximal dimension of tumor, based on pathologic measure or clinical measure if no pathologic measure given
8. Lymph nodes – yes, no or not known; based on pathologic microscopic examination of lymph nodes removed and records any lymph nodes with tumor deposits as yes. Patients who did not have removal of lymph nodes are considered to be unknown.
9. Lymph node group – categorizes all patients as to the number of individual lymph nodes containing tumor deposits. (unknown, no lymph nodes positive, 1 to 3 lymph nodes positive, or more than 3 lymph nodes positive)
10. Treatment Group – categorizes all patients into one of three groups according to the type of treatment received (standard therapy, neo-adjuvant chemotherapy, and other)
11. Surgery Type – classifies patients according to type of surgery (mastectomy, segmental mastectomy or none)
12. Chemotherapy – records if patient has received chemotherapy at any point in their treatment (0 or 1)
13. Hormone therapy – records if patient has received hormone therapy at any point in their treatment (0 or 1)

Baseline patient characteristics for the study population, patients with LABC, are summarized for the various disease stages and groups treated with different combinations of modalities. Kaplan-Meier estimates [70] were used to analyze the survival data from the date of diagnosis of LABC to either date of death or last date of follow-up (last possible follow-up was June 1, 2002)[1]. Survival curves, utilizing overall or breast cancer specific mortality, for the various baseline characteristics, disease stages, and different treatment groups are compared using the log-rank test. A Cox proportional hazards model [70] was fit to create a regression model that included all available explanatory variables. Appropriate interaction terms were tested in the model.

A calculated p-value of less than 0.05 is considered statistically significant for all statistical tests in this study. Stata (version 7), (Stata® Corp.) was used for all statistical analyses for this portion of the project.

B. Development of a Decision Analysis Framework for Locally Advanced Breast Cancer Treatment Options

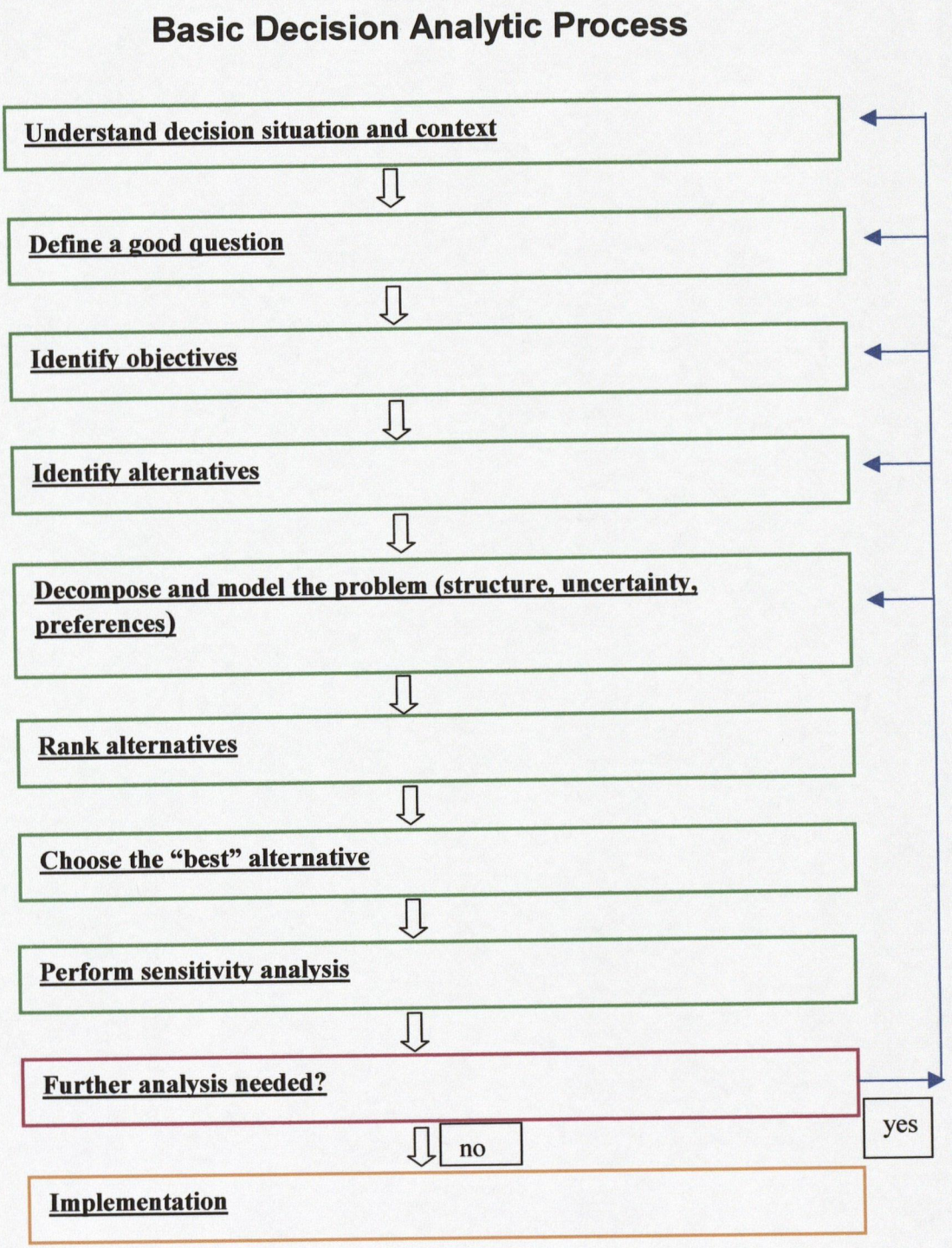
This portion of the study involves a discussion of the following issues to provide a framework for the development of a decision analysis model for treatment options in LABC patients:

1. Description of the underlying theory of decision analysis.
2. Description of the target audience for the analysis and stakeholders
3. Choice of outcome measures and their rationale
4. Development of a model structure and rationale for this structure
5. Description of time frame and its incorporation into the model
6. Estimation of probabilities and utilities
7. Uncertainty and sensitivity analysis method
8. Issues of discounting health

[1] The ACR was last linked with the Alberta Health Registry for censoring data in December, 1999 to provide potential losses to follow-up from inactivation of Alberta Health Care Insurance numbers. A new update was supposed to be available for this study, but has yet to be produced. For the purpose and scope of this study we will assume that loss to follow-up data is included with the current data files up to June, 2002, but we do recognize that a small number of patients may not be appropriately censored in this study (only 11 patients were lost to follow-up from January, 1994 to December, 1999).

The flowchart in Figure 4 shows the process that was followed in the development of the decision analysis framework. Although this is the process by which one would complete a decision analysis, the current project moved through this flow diagram to describe the issues in general and those issues directly related to the treatment strategies in LABC to provide a framework for the complete decision analysis.

Figure 4 - Decision Analysis Process Flowchart
(modified from Clemen 1996 and Lee 2001)



V. Results: Survival Analysis

Part A - General Characteristics

Patient Characteristics:

A total of 3780 female patients were identified from ACR data that had a new diagnosis of a primary invasive breast carcinoma between January 1, 1994 and December 31, 1996. A total of 467 subjects were excluded from the study due to the diagnosis of another cancer, except non-melanoma skin cancer. This left 3313 patients for consideration in the study. There are a total of 499 patients who fit the criteria for LABC, primary tumor > 3.0 cm and/or N2 disease. Seven patients were excluded because they did not have complete data. This left a total of 492 LABC patients with complete data; they are included as the study population. See Table 5 for general characteristics of the LABC study population.

Age:

The average age of the study patients is 56.8 years, with a range of 17 to 97 years.

Stage:

The study population, as a whole, has near equal proportions in each stage considered as LABC. The patients treated with standard therapy have a greater proportion of women in stage 2A (26% versus 5%) (p=0.001) and 2B (41% versus 27%) (p=0.02) when compared to women treated with neo-adjuvant chemotherapy. Women treated with neo-adjuvant chemotherapy have a greater proportion of patients in stage 3B (47% versus 11%) (p<0.001) when compared to patients treated with standard therapy.

Tumor Size:

The size of a tumor is measured in centimetres (cm) and the distance of the greatest dimension is recorded. The mean size of tumors in the study population is 4.5 cm (standard deviation = 1.9 cm), with a range of 0 to 12 cm. Table 6 shows the mean tumor size by TNM stage.

Table 5 – General Characteristics for Study Population of LABC Patients in Alberta 1994-1996

	Total Study Population (%) (n=492)	*Standard Therapy (%) (n=379)*	*Neo-Adjuvant Chemotherapy (%) (n=75)*
Mean Age (range)	56.8 years (17-97 years)	57.6 years (17-95 years)	49.2 years (26-84 years)
< 30 years	8 (2)	6 (2)	2 (2)
30 – 50 years	173 (35)	119 (31)	39 (52)
50 – 70 years	192 (39)	160 (42)	29 (39)
> 70 years	119 (24)	94 (25)	5 (7)
Mean Tumor Size (range) (cm)	4.5 cm (0 – 12 cm)	4.2 cm (0.6 – 12 cm)	5.6 cm (0 – 10.5 cm)
0 – 2 cm	25 (5)	14 (4)	8 (11)
2 – 5 cm	300 (61)	261 (69)	24 (32)
5 – 10 cm	153 (31)	100 (26)	35 (46)
> 10 cm	14 (3)	4 (1)	8 (11)
TNM Stage			
2A	106 (22)	98 (26)	4 (5)
2B	181 (37)	157 (41)	20 (27)
3A	110 (22)	82 (22)	16 (21)
3B	95 (19)	42 (11)	35 (47)
Histologic Grade			
1	55 (11)	45 (12)	6 (8)
2	205 (42)	160 (42)	28 (37)
3	232 (47)	174 (46)	41 (55)
Lymph Nodes			
Negative	123 (25)	121 (32)	1 (1)
Positive	257 (52)	233 (61)	6 (8)
Unknown	112 (23)	25 (7)	68 (91)
1 to 3 nodes positive	140 (28)	129 (34)	3 (4)
> 3 nodes positive	117 (24)	104 (27)	3 (4)
Hormone Therapy			
Yes	215 (44)	173 (46)	25 (33)
No	277 (56)	206 (54)	50 (67)
Surgery Type			
Mastectomy	311 (63)	267 (70)	31 (41)
Segmental Mastectomy	133 (27)	112 (30)	17 (23)
None	48 (10)	0 (0)	27 (36)

Table 6 - Mean Tumor Size by TNM Stage for LABC Patients 1994-1996

AJCC TNM Disease Stage	*Mean Tumor Size (cm)*	*Number (%) (n=492)*
2A	3.9	106 (22)
2B	4.4	181 (37)
3A	5.3	110 (22)
3B	4.4	95 (19)

No trend in tumor size is identified when the data is stratified by Stage of Disease.

The size of tumors treated with neo-adjuvant chemotherapy is larger than the size of tumors treated by standard therapy. The mean size of tumors treated with neo-adjuvant chemotherapy is 5.6 cm (sd = 2.7 cm) and the mean size of tumors treated with standard therapy is 4.2 cm (sd=1.5 cm) ($p < 0.001$). Tumors treated by mastectomy are larger (mean = 4.6 cm) than those treated by segmental mastectomy (mean = 4.1 cm) (p=0.0088).

Histological Grade:

The histological grade of a tumor is a "ranking of malignancy" based on the microscopic appearance of the tumor. The most common grading system is the modified Bloom-Richardson score. It grades the tumors based on 3 microscopic features, architectural (tubule formation), nuclear pleomorphism (differentiation) and mitotic activity (cell division) [23]. It is scored as 1, 2 or 3, with 1 being low grade (best prognosis) and 3 being high grade (worst prognosis) [23]. The study population's histological grade distribution has increasing proportions in higher-grade categories. Only 11% are grade 1, and almost half, 47%, are grade 3 tumors. The distribution of histological grade by TNM stage is shown in the Table 7 below. There is no trend identified, as there are similar distributions of histological grade in each TNM stage.

Table 7 - Distribution of Histologic Grade by Stage for LABC Patients in Alberta, 1994-1996

AJCC TNM Disease Stage	*Histologic Grade 1 Number (percent of stage total)*	*Histologic Grade 2 Number (percent of stage total)*	*Histologic Grade 3 Number (percent of stage total)*
2A (n=106)	13 (12)	37 (35)	56 (53)
2B (n=181)	20 (11)	75 (41)	86 (48)
3A (n=110)	11 (10)	50 (45)	49 (45)
3B (n=95)	11 (12)	43 (45)	41 (43)

Lymph Nodes:

Tumor cells can spread to the axillary lymph nodes, and when these are removed at the time of surgery they are examined microscopically to determine if the lymph node has any identifiable tumor cell deposits. If a lymph node contains a tumor cell deposit, it is considered a "positive node". When no surgery is performed or lymph nodes are not removed at the time of surgery, the nodal status of the patient is unknown, not negative and not positive. 257 (52%) of the study population have positive lymph nodes. Of those with positive lymph nodes, 140 (54%) have between 1 and 3 positive nodes and 117 (46%) have more than 3 lymph nodes that show evidence of tumor cell deposits. Twenty three percent of the patients included in the study population have an unknown lymph node status from either receiving no surgery or no lymph nodes were removed at the time of surgery. Only 7% of patients who received standard therapy, which always includes surgery, have an unknown lymph node status. Over 90% of patients treated with neo-adjuvant chemotherapy protocols, which included surgery in 64%, are recorded as having no lymph nodes removed. This is likely explained by the fact that when neo-adjuvant chemotherapy is given it will destroy tumor cells in both the primary tumor of the breast and other focuses of metastatic tumor, i.e. tumor that may be in the lymph nodes. Thus, patients who receive neo-adjuvant chemotherapy will have their lymph nodes "treated" prior to removal. Removal of lymph nodes at this point for staging purposes would

"incorrectly" stage these patients, and thus lymph node status should not be used in a prognostic manner as it is in the standard therapy patients.

Treatment Modalities:

A total of 10 different strategies were identified for the treatment of breast cancer in our study population (see Table 8) depending on the type and order of treatments given. These different regimens can be grouped into common strategies. The patients that received local treatment, surgery and/or radiation therapy, or local treatment followed by systemic chemotherapy can be grouped into the standard treatment group (standard). Patients treated with chemotherapy first, prior to other local treatments, can be grouped into the neo-adjuvant chemotherapy group (neo-adjuvant). There are a number of other treatment regimens used including high dose chemotherapy and stem-cell transplant, unimodality treatment with radiation or hormone therapy, which do not fit common multimodality regimens. These likely represent treatment selection based on tumor or patient characteristics or preferences that are non-standard. They makeup 8% of the patients and will be included as a group in a separate category (other).

Table 8 - Identified Treatment Regimens and Classification by Treatment Group for LABC Patients Treated in Alberta, 1994-1996

	Treatment Regimen	*Treatment Group*	*Number (n=492) (%)*
1	S → +/- H	Standard	168 (34)
2	S → CT → +/- H	Standard	211 (42)
3	CT → +/- H	Neo-Adjuvant	8 (2)
4	CT → RT → +/- H	Neo-Adjuvant	19 (4)
5	CT → S → +/- RT → +/- H	Neo-Adjuvant	48 (9)
6	S → T	Other	9 (2)
7	T → S	Other	8 (2)
8	RT Only	Other	8 (2)
9	H Only	Other	9 (2)
10	None	Other	4 (1)

Abbreviations:
S - surgery
CT - chemotherapy
RT - radiation therapy
H - hormone therapy
T – transplant therapy
→ - indicates sequential use of various modalities

In the group of patients with LABC, 444 (90%) patients received surgery, mastectomy (63%) or segmental mastectomy (27%), at some point in their therapy. 303 (61%) women received chemotherapy at some point in their treatment. A total of 75 (15%) patients with LABC were treated with neo-adjuvant chemotherapy. 215 patients (56%) were treated with hormone therapy, drug therapy directed towards interruption of estrogen or progesterone functioning (e.g. Tamoxifen).

Hormone Therapy:

The use of hormone therapy did not vary according to stage (Chi^2, $p = 0.71$), as would be expected. The use of hormone therapy is associated with estrogen and progesterone receptor status of the tumor, which is not associated with stage of disease (see Table 9).

Table 9 - The Use of Hormone Therapy by Stage of Disease in LABC Patients from Alberta, 1994-1996

TNM Stage	*Hormone treatment – No (%) (n=277)*	*Hormone treatment – Yes (%) (n=215)*
2A	65 (23)	41 (19)
2B	100 (36)	81 (38)
3A	60 (22)	50 (23)
3B	52 (19)	43 (20)

Treatment Type by Disease TNM Stage:

As disease stage (TNM) increases there are greater proportions of patients treated with neo-adjuvant chemotherapy or other, non-standard, therapies; and conversely fewer patients treated with standard therapy.

Table 10 - The Treatment Type Used for LABC Patients by Stage of Disease in Alberta, 1994-1996

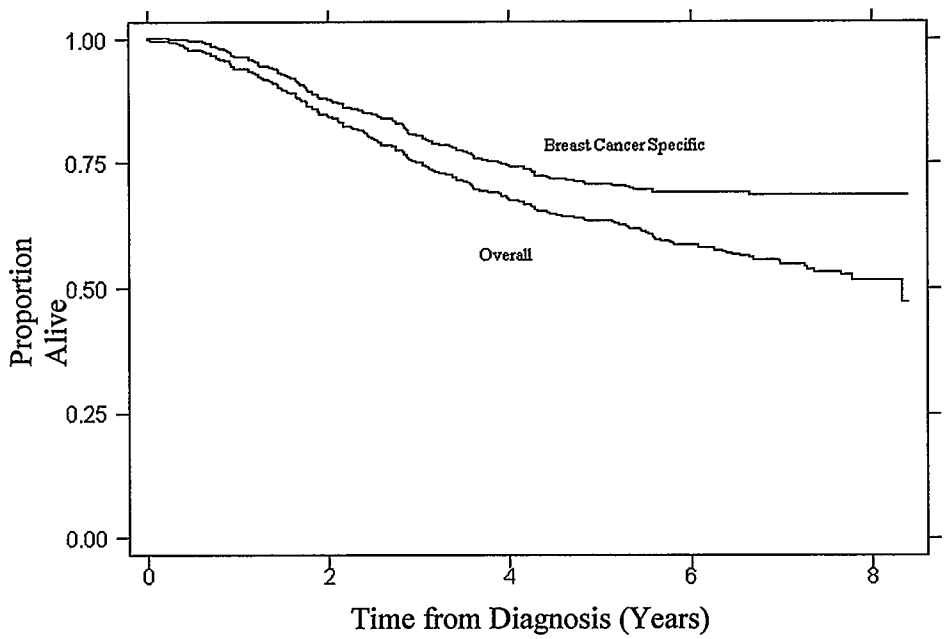
TNM Stage	*Standard Therapy (%) (n=379)*	*Neo-Adjuvant Chemotherapy (%) (n=75)*	*Other Therapy (%) (n=38)*
2A	98 (26)	4 (5)	4 (11)
2B	157 (41)	20 (27)	4 (11)
3A	82 (22)	16 (21)	12 (31)
3B	42 (11)	35 (47)	18 (47)

B. Survival Characteristics

Overall and Breast Cancer Specific Survival:

The overall 5-year survival is 63% (95% CI 58.7 – 67.3), and 8-year survival is 52% (95% CI 46.3 – 56.7). The breast cancer specific 5-year survival is 70% (95% CI 66.0 – 74.4), and 8-year breast cancer specific survival is 68% (95% CI 63.9 – 72.5) for the study population of women with LABC (see Figure 5). Overall mortality for women is higher than mortality from breast cancer causes. The mean age at diagnosis of women in the study population is 56.8 years with almost one quarter of women being age 70 or over, a population will at risk for many causes of mortality. Although overall mortality is higher, breast cancer specific causes of death account for a large proportion (75% of deaths at 8 years) of the mortality causes in this study population.

Figure 5 - Overall and Breast Cancer Specific Kaplan-Meier Survival for Women Diagnosed with LABC in Alberta, 1994-1996



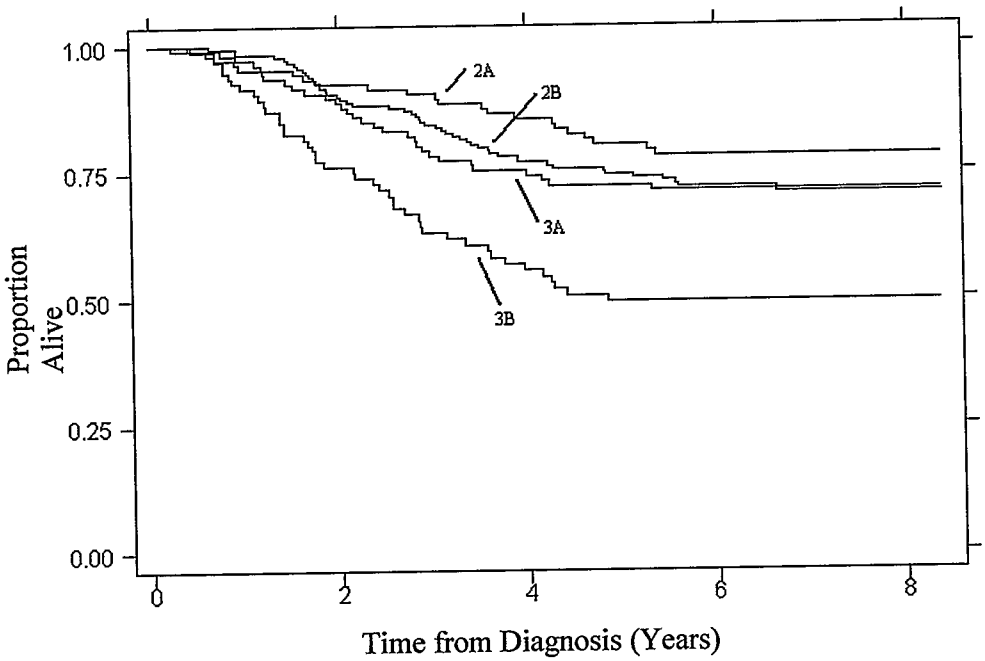
Numbers at risk

	492	415	333	245	54

Effect of Stage of Disease on Breast Cancer Survival:

There are differences in breast cancer specific mortality for women when stratified by disease stage (log-rank, $p<0.001$) (see Figure 6). Patients with higher stage of disease have a higher mortality. Because the TNM staging system was designed around stratification of patients according to survival characteristics, the differences in the survival is expected. The 8-year survival for women with stage 2A is 78% (95% CI 68.5 – 85.0), stage 2B is 70.6% (95% CI 62.9 – 77.0), stage 3A is 71.1% (95% CI 61.3 – 78.9), and for 3B is 49.4% (95% CI 38.3 – 59.5).

Figure 6 - Breast Cancer Related Kaplan-Meier Survival by Stage of Disease for Women Diagnosed with LABC in Alberta, 1994-1996



Number at risk					
2A	106	96	84	62	10
2B	181	161	132	92	17
3A	110	94	76	58	10
3B	95	68	46	25	7

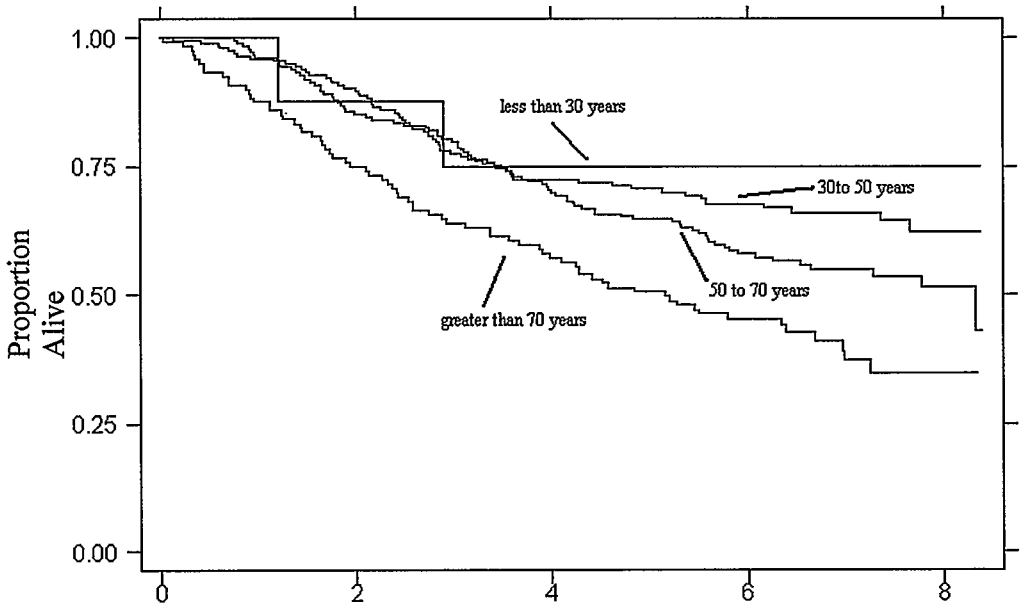
Effect of Age at Diagnosis on Overall and Breast Cancer Specific Survival:

The continuous age variable was separated into four categories, less than 30 years, 30 to 50 years, 50 to 70 years and more than 70 years of age at diagnosis of LABC. These categories were chosen to separate patients into clinically relevant age categories. The less than 30 years category represents young patients who generally present with higher stage disease [71]. The category of 30 to 50 years represents the pre-menopausal group of women who have a different hormonal profile than post-menopausal women [71, 72]. The 50 to 70 years category captures the post-menopausal group; and the greater than 70 years group represents patients who are at risk of many other time dependent causes of mortality. Women under the age of 70 years at diagnosis have similar survival until about the fourth year of follow-up when mortality for older groups increases (see Figure 7). Women greater than 70 years of age at diagnosis have an increased overall mortality right from the start of follow-up when compared to women under age 70 (log rank, p=0.001). 5-year survival for women less than 70 years of age ranges from 65% to 75%, with women greater than 70 years of age at 50% (95% CI 41.1 – 59.0) (see Table 11). At 8 years of follow-up, the survival rate for women less than 30 years of age is 75% (95% CI 31.4 – 93.1), for women age 30 – 50 years it is 62.1% (95% CI 52.9 – 70.0), for women age 50 – 70 years it is 51.5% (95% CI 42.9 – 59.3) and for women age more than 70 years it is only 34.7% (95% CI 24.5 – 45.0).

Table 11 - Five and Eight Year Overall Survival Stratified by Age at Diagnosis for Women with LABC in Alberta, 1994-1998

	Age at Diagnosis (years)	Percent Survival	95% Confidence Interval
5-year survival	< 30	75.0	31.4 – 93.1
	30 – 50	70.5	63.1 – 76.7
	50 – 70	64.6	57.3 – 70.9
	> 70	50.4	41.1 – 59.0
8-year survival	< 30	75.0	31.4 – 93.1
	30 – 50	62.1	52.9 – 70.0
	50 – 70	51.5	42.9 – 59.3
	> 70	34.7	24.5 – 45.0

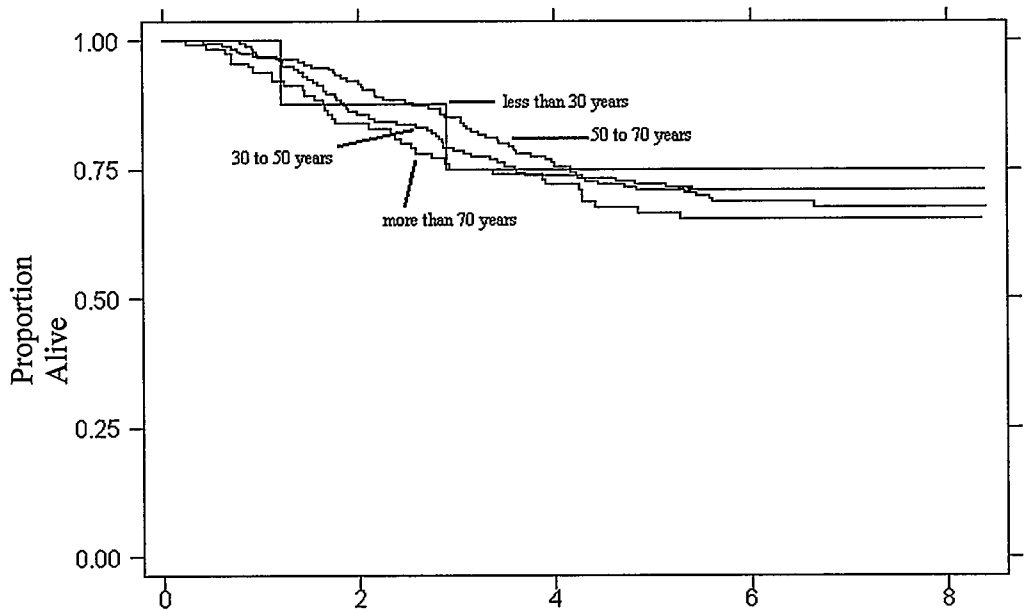
Figure 7 – Overall Kaplan-Meier Survival by Age for Women Diagnosed with LABC in Alberta, 1994-1996



Number at risk					
< 30 yrs	8	8	7	6	3
30-50 yrs	173	148	126	98	15
50-70 yrs	192	173	135	86	20
> 70 yrs	119	90	69	47	6

Breast cancer specific mortality, when stratified by age at diagnosis, is similar for all age groups (log rank, p=0.751) (see Figure 8). The 8-year survival for women less than 30 years of age is 75% (95% CI 31.4 – 93.1), for women age 30 – 50 years is 70.8% (95% CI 63.3 – 77.0), for women aged 50 – 70 years is 67.5% (95% CI 59.9 – 73.9), and for women greater than 70 years of age it is 65.4% (95% CI 55.2 – 73.8). For the women with LABC in the study, overall mortality increases with age, but age is not a factor for breast cancer specific deaths.

Figure 8 - Breast Cancer Specific Kaplan-Meier Survival by Age for Women Diagnosed With LABC in Alberta, 1994-1996



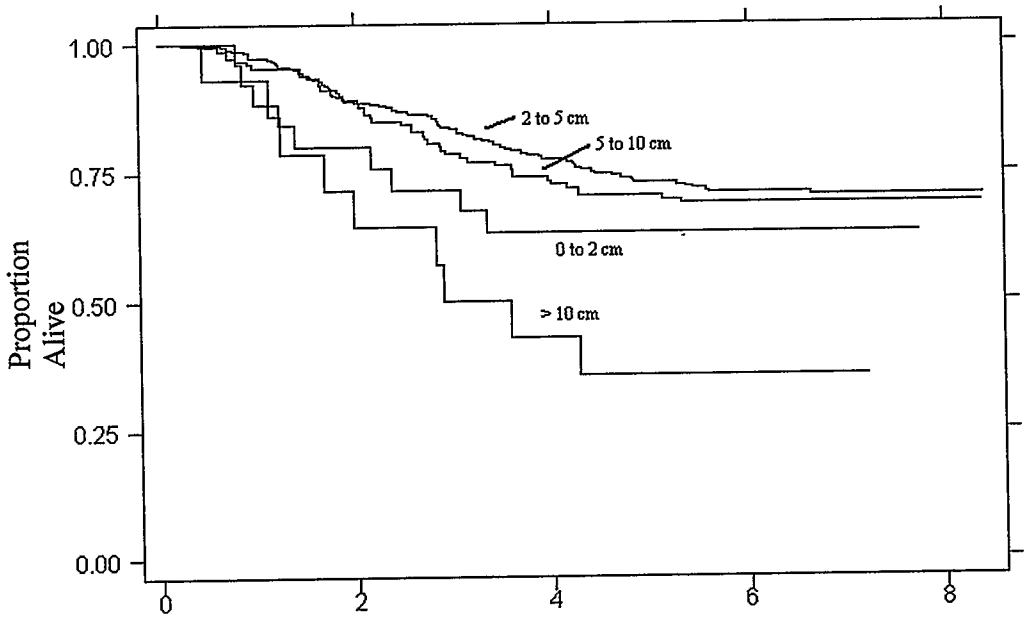
Number at risk

< 30 yrs	8	8	7	6	3
30-50 yrs	173	148	126	98	15
50-70 yrs	192	173	135	86	20
> 70 yrs	119	90	69	47	6

Effect of Tumor Size on Breast Cancer Survival:

Tumor size is categorized into four groups according to size criteria of the TNM stage classification, and tumors greater than 5 cm were divided into two groups. The resulting size categories are: 0 to 2 cm, 2 to 5 cm, 5 to 10 cm, and greater than 10 cm. 8-year survival for women with tumors 2 to 5 cm is 70.2% (95% CI 64.3 – 75.2), which is similar to women with tumors 5 to 10 cm whose 8-year survival is 68.9% (95% CI 60.4 – 75.8). Women with the smallest tumors, 0 to 2 cm, have an 8-year survival of only 63.2% (95% CI 41.0 – 78.9). For these small tumors to be considered locally advanced they must have significant amounts of tumor in the lymph nodes, which may suggest a higher probability of occult metastatic disease at the time of diagnosis and treatment. It should be noted that the numbers of at risk women with tumors 0 to 2 cm is small (only 25 to start), and that survival differences with women whose tumors are between 2 and 10 cm is not significant (overlapping 95% confidence intervals). Women with tumors of the greatest size, greater than 10cm, have the poorest 8-year survival of 35.7% (95% CI 13.0 – 59.4) (log-rank, p=0.001) (see Figure 9).

Figure 9 - Breast Cancer Specific Kaplan-Meier Survival by Tumor Size for Women Diagnosed With LABC in Alberta, 1994-1996

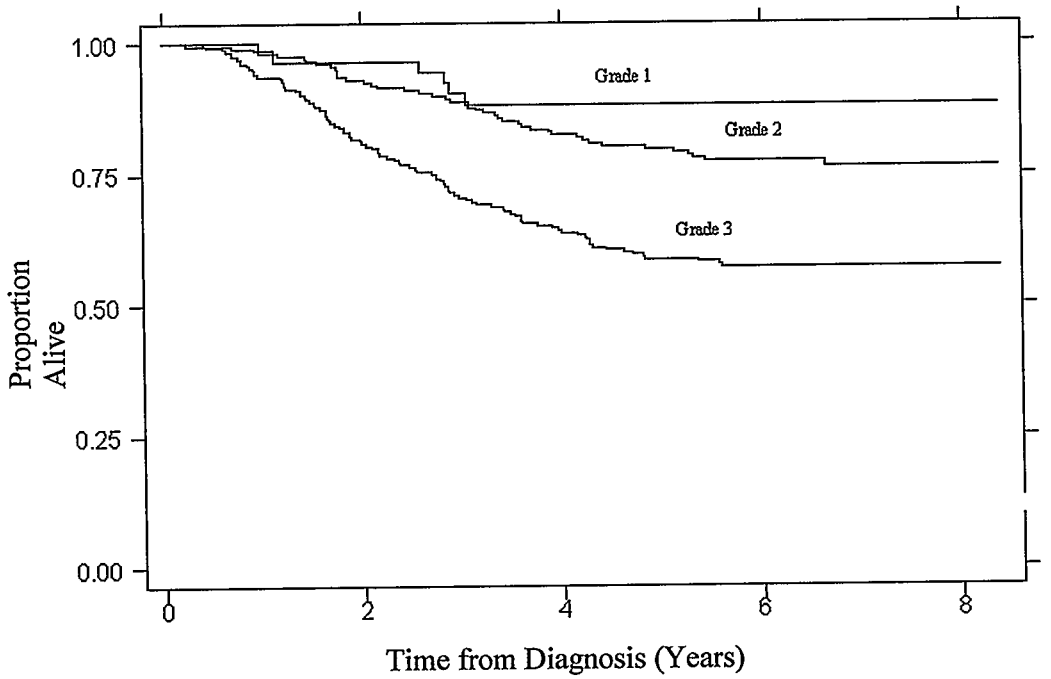


Number at risk					
0 – 2 cm	25	20	16	13	1
2 – 5 cm	300	260	214	148	32
5 – 10 cm	153	129	100	72	10
> 10 cm	14	10	7	4	1

Effect of Histological Grade on Breast Cancer Survival:

Women tend to have poorer survival with increasing histologic grade of their tumor (log rank, $p<0.001$) (see Figure 10). Women with grade 1 tumors have an 8-year survival of 88.3% (95% CI 75.6 – 94.6), women with grade 2 tumors 76.2% (95% CI 69.1 – 81.8), and women with grade 3 tumors 57.2% (95% CI 50.3 – 63.4). Histological grade appears to be an important factor in breast cancer specific survival in our study population of patients with LABC.

Figure 10 - Breast Cancer Specific Kaplan-Meier Survival by Histologic Grade for Women Diagnosed With LABC in Alberta, 1994-1996



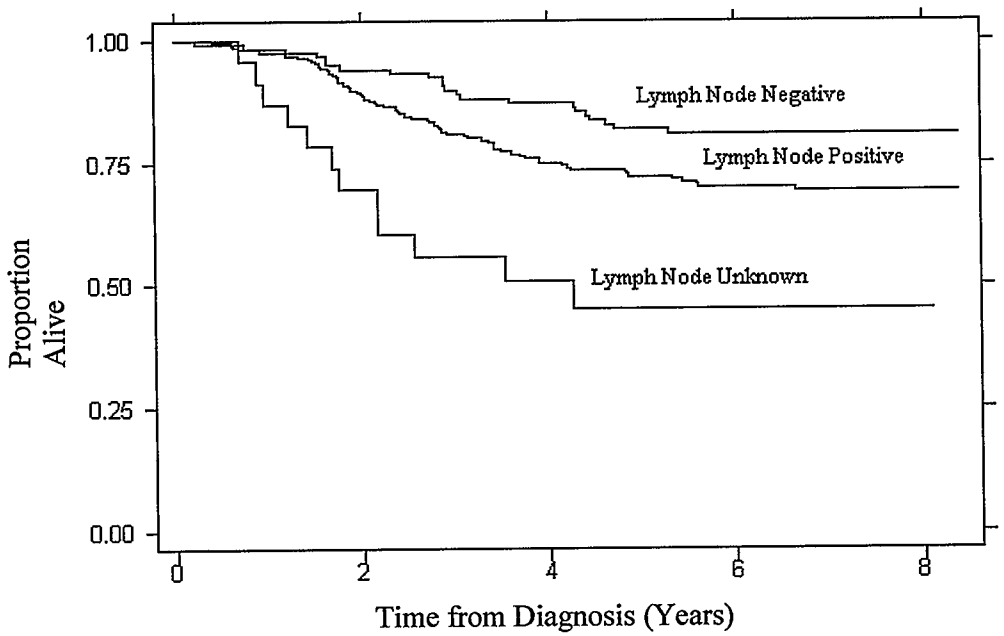
Number at risk					
Grade 1	55	52	45	36	4
Grade 2	205	183	151	103	19
Grade 3	232	183	140	97	20

Effect of Lymph Node Status on Breast Cancer Survival:

As identified earlier, we cannot use lymph node status as a prognostic variable in women treated with neo-adjuvant chemotherapy. For women treated with standard therapy, the staging of patients based on lymph node status is accurate. In women patients treated with standard therapy, lymph node negative women have a better prognosis than those with positive lymph nodes (log rank, p=0.022); and both lymph node negative and positive women have better survival than those women whose lymph node status is unknown (log rank, p=0.001) (see Figure 11). 8-year survival for women treated with standard therapy and have no tumor in their lymph nodes is 81.0% (95% CI 72.6 – 87.1), for women with tumor in their lymph nodes 69.3% (95% CI 62.6 – 75.0); and, for women with uncertain lymph node status it is 45.4%

(95% CI 23.9 – 64.6). In our study population, lymph node status is an important prognostic factor for women treated with standard therapy.

Figure 11 - Breast Cancer Specific Kaplan-Meier Survival by Lymph Node Status for Women with LABC Treated with Standard Therapy



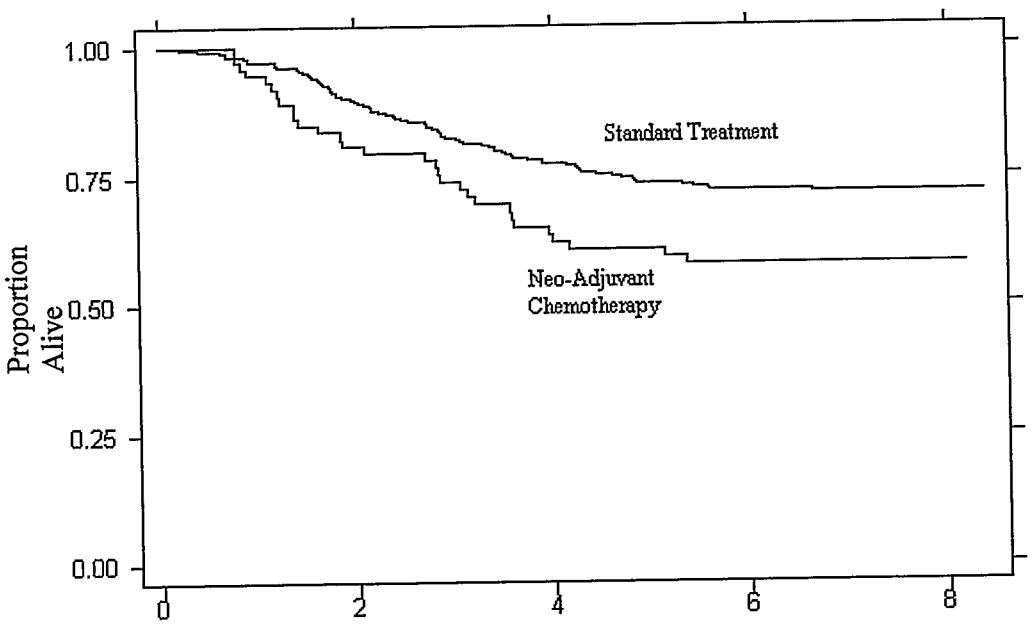
Number at risk					
Negative	121	113	101	77	4
Positive	233	202	163	120	24
Unknown	25	16	10	5	2

Effect of Treatment Type Received on Breast Cancer Survival:

Figure 12 shows the breast cancer specific survival curves for patients treated with either neo-adjuvant chemotherapy strategies or standard therapy strategies. When other important factors are not considered, women who were treated with neo-adjuvant chemotherapy regimens had decreased survival when compared to women treated with standard therapeutic regimens (log rank, p=0.01). The 8-year survival for women treated with neo-adjuvant chemotherapy is 57.8% (95% CI 45.3 – 68.3), and for women treated with standard therapy is 71.6% (95% CI 66.6 – 76.1). There are differences between the two treatment groups that are not included in this simple

comparison. It is possible that the choice of treatment is based upon patient and tumor factors which have an implication on prognosis or survival, i.e. confounding by indication. If patients are chosen for a particular treatment based on the factor we are trying to measure (i.e. survival), then the apparent difference in that factor seen between treatments is not a result of the treatment in similar groups, but a result of the groups being different in the characteristic of interest (i.e. survival). To limit the potential of "confounding by indication" the difference in survival of women between the two treatment groups can be examined while controlling for other factors that may impact survival, this is reported later in the results section for the Cox model.

Figure 12 - Breast Cancer Specific Kaplan-Meier Survival by Treatment Type Received for Women Diagnosed with LABC in Alberta, 1994-1996

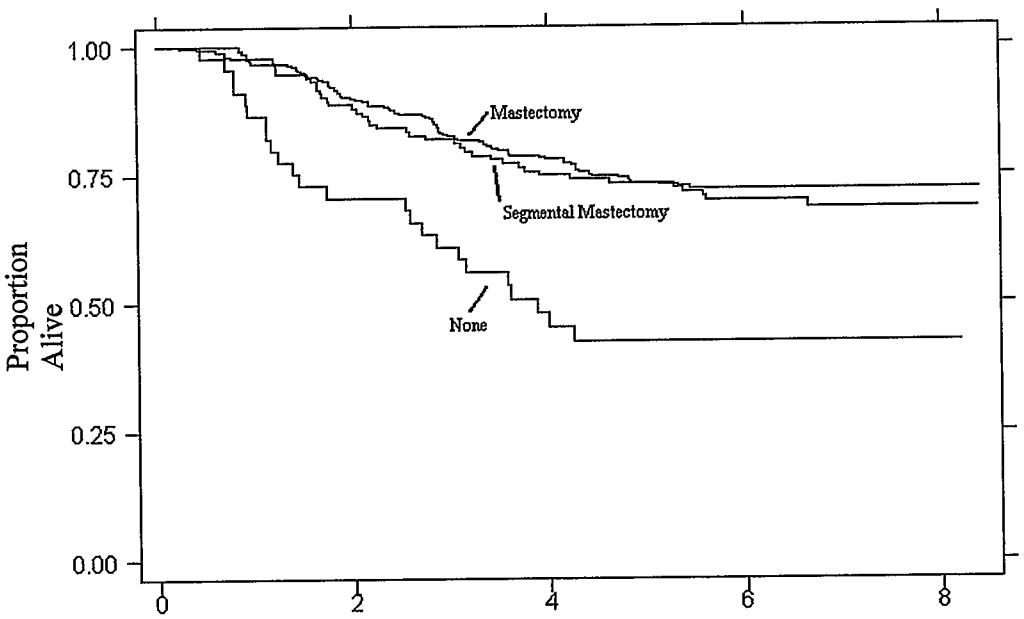


Number at risk					
standard	379	329	271	199	35
neo-adjuvant	75	59	44	27	6

Effect of Surgery Type Received on Breast Cancer Survival:

Women who are treated with a mastectomy have a similar mortality to the women who are treated with a segmental mastectomy and radiation therapy (log rank, p=0.53). There is a survival difference in women who are treated with surgery versus those who are not treated with surgery (log rank, p<0.001). These results confirm others findings that survival is similar in patients receiving mastectomy or segmental mastectomy with radiation therapy [73]. The 8-year survival in women treated with mastectomy is 72.1% (95% CI 66.5 – 76.9), for women treated with segmental mastectomy and radiation therapy is 68.5% (95% CI 59.5 – 75.9), and for women who receive no surgical therapy is 42.3% (95% CI 26.9 – 56.7).

Figure 13 - Breast Cancer Specific Kaplan-Meier Survival by Surgery Type Received for Women Diagnosed with LABC in Alberta, 1994-1996

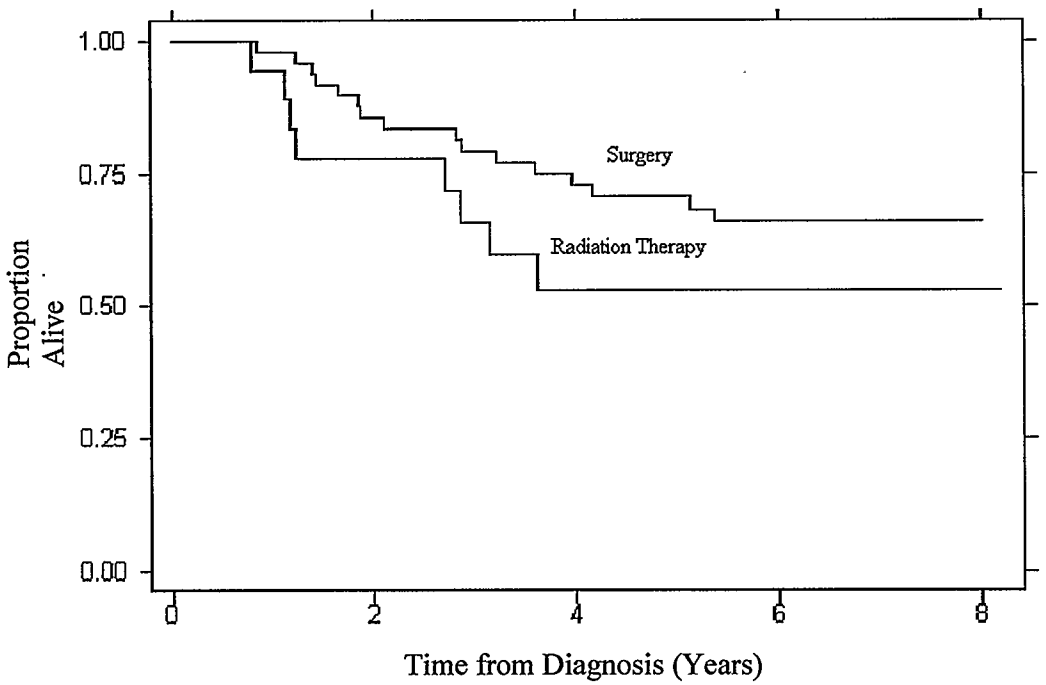


Number at risk					
Mastectomy	311	271	224	157	24
Segmental	133	116	95	69	15
None	48	31	17	10	4

Local Treatment After Neo-Adjuvant Chemotherapy:

Of the patients treated with neo-adjuvant chemotherapy (n=75), 48 patients had surgery after treatment, 19 had radiation therapy, and 8 patients had no further therapy beyond chemotherapy. Women who received surgery following neo-adjuvant chemotherapy have an 8-year survival of 66.1% (95% CI 50.7 – 77.7) and women who received radiation therapy after neo-adjuvant chemotherapy have an 8-year survival of 53.2% (95% CI 27.5 – 73.4) (log rank, p=0.2253).

Figure 14 - Breast Cancer Specific Kaplan-Meier Survival for Women with LABC Treated with Neo-Adjuvant Chemotherapy by Follow-up Treatment Received



Number at risk

Surgery	48	42	35	20	3
Radiation	19	14	9	8	4

Breast Conservation:

Breast conserving therapy can be defined as therapy for the treatment of breast cancer that results in preservation of, at least a portion of, the affected breast. In the present

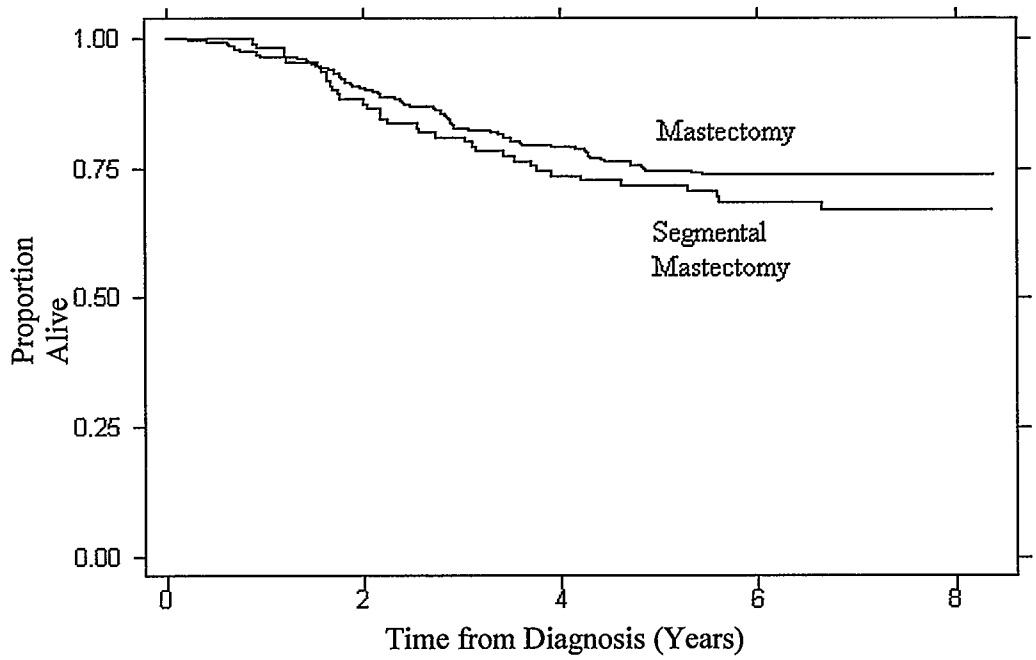
study, breast-conserving therapies are considered segmental mastectomy or no surgery. The study population results show that breast conservation was achieved in 112 of 379 (30%) patients treated with standard therapy and in 44 of 75 (59%) patients treated with neo-adjuvant chemotherapy (see Table 12). The use of neo-adjuvant chemotherapy in the study population of LABC patients significantly increased the proportion of breast conserving therapies used ($p<0.001$).

Table 12 - Surgery Type Performed on Women with LABC by Treatment Group

Surgery type performed	*Neo-Adjuvant Chemotherapy (%) (n=75)*	*Standard Therapy (%) (n=379)*
Mastectomy	31 (41)	267 (70)
Segmental Mastectomy	17 (23)	112 (30)
None	27 (36)	0 (0)

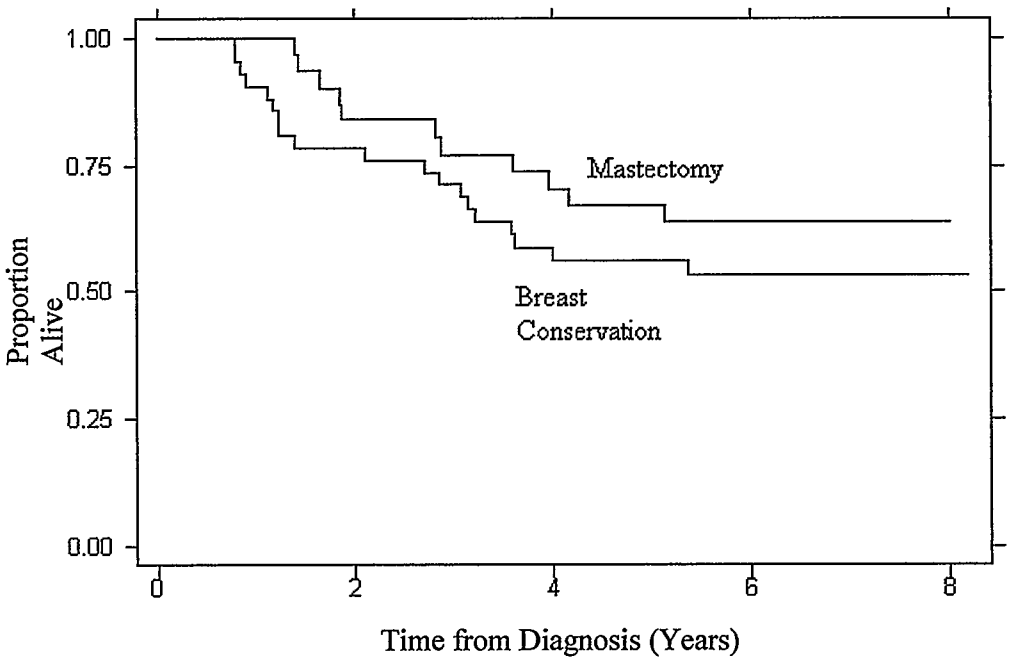
For patients treated with standard therapy, survival is similar between women treated with mastectomy and women treated with breast conserving therapy (log rank, $p=0.26$)(see Figure 15). The 8-year survival for women treated with standard therapy and a mastectomy is 73.7% (95% CI 67.7 – 78.2); and for women treated with breast conservation is 67.0% (95% CI 56.9 – 75.2). For patients treated with neo-adjuvant chemotherapy, survival for women treated with breast conserving therapies is similar to those treated with a mastectomy (log rank, $p = 0.29$) (see Figure 16). The 8-year survival for women treated with neo-adjuvant chemotherapy and a mastectomy is 63.7% (95% CI 44.1 – 78.1) and for women treated with breast conservation is 53.4% (95% CI 36.9 – 67.3).

Figure 15 - Breast Cancer Specific Kaplan-Meier Survival for Women with LABC Treated with Standard Therapy by Surgery Type



Number at risk					
Mastectomy	267	233	194	141	23
Segmental	112	97	78	59	13

Figure 16 - Breast Cancer Specific Kaplan-Meier Survival for Women with LABC Treated with Neo-Adjuvant Chemotherapy by Mastectomy versus Breast Conserving Therapy

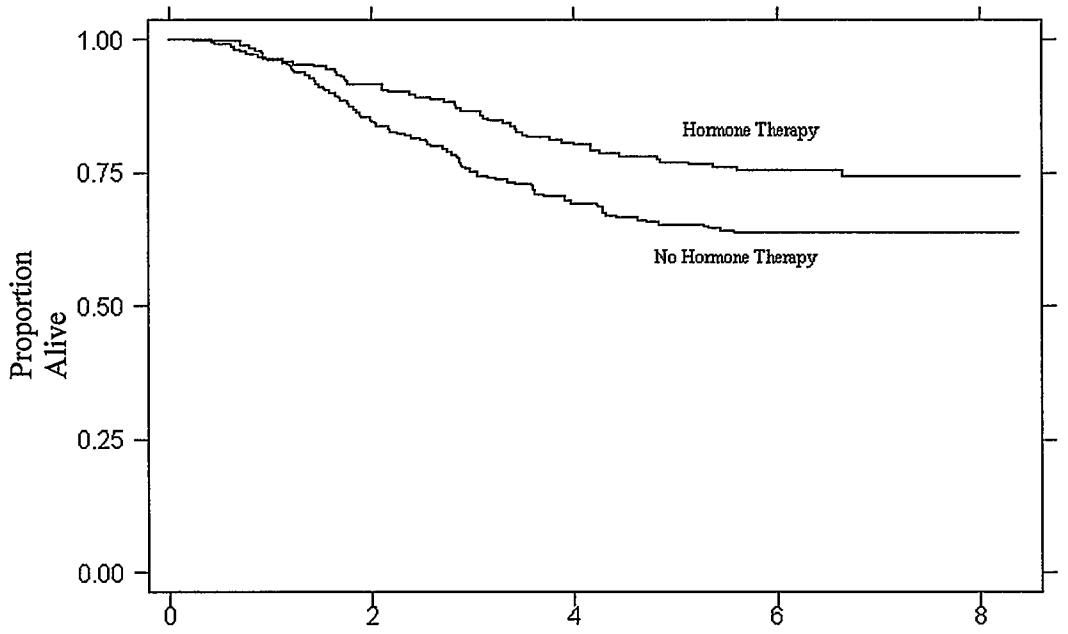


Number at risk					
Mastectomy	31	27	22	14	2
Conservation	44	33	23	14	5

Effect of Hormone Therapy on Breast Cancer Specific Survival:

Figure 17 shows the breast cancer specific survival of LABC patients treated with and without hormone therapy. Patients treated with hormone therapy have superior survival when compared to women not treated with hormone therapy (log rank, p=0.0085). The 8-year survival for hormone treated patients is 74.3% (95% CI 67.5 – 79.9) and the 8-year survival for patients not treated with hormone therapy is 63.8% (95% CI 57.6 – 69.3).

Figure 17 - Breast Cancer Specific Kaplan-Meier Survival by Hormone Therapy for Women Diagnosed with LABC in Alberta, 1994-1996



Number at risk					
Hormone	215	190	158	108	21
No hormone	277	227	177	127	21

C. Cox Model

1. Cox Model

A Cox proportional hazards regression model was used to test the study variables that may explain differences in breast cancer specific survival (explanatory variables). This analysis was restricted to the 454 women who received either neo-adjuvant therapy (n=75) or standard therapy (n=379). Variables that were included in the model were selected from the available data. The initial Cox model included the variables for: patient age at diagnosis, disease stage, histologic grade, tumor size, hormone treatment, treatment type (neo-adjuvant chemotherapy versus standard therapy) and surgery type (see Table 13). In the first model, interaction terms were tested for the variables of disease stage versus tumor size, and treatment type versus

surgery type. The first interaction term was tested because the size of the tumors is also included as a part of disease stage determination and therefore they may vary in the same way. The second interaction term was tested because the type of surgery was different for the standard therapy versus neo-adjuvant treated patients. None of the interaction terms were found to be significant ($p>0.05$) in the fitted model.

Table 13 - Cox Proportional Hazards Model of Breast Cancer Specific Survival for Women with LABC Using Selected Variables

Variables in Cox Model	*Hazard Ratio*	*p-value*	*95% Confidence Interval*
Stage 2B (vs. 2A)	1.78	0.037	1.03 – 3.06
Stage 3A (vs. 2A)	2.24	0.009	1.21 – 4.13
Stage 3B (vs. 2A)	4.72	<0.001	2.49 – 8.92
Grade 2 (vs. Grade 1)	3.70	0.029	1.13 – 12.0
Grade 3 (vs. Grade 1)	8.92	<0.001	2.80 – 28.4
Hormone Treatment (vs. no hormone treatment)	0.62	0.019	0.42 – 0.92
Standard Therapy (vs. neo-adjuvant chemo)	1.24	0.466	0.69 – 2.23
Tumor Size	1.02	0.593	0.93 – 1.12
Age at Diagnosis	1.01	0.394	0.99 – 1.02
Mastectomy (vs. Segmental Mastectomy)	1.22	0.326	0.82 – 1.80

The hazard ratios produced by the Cox model can be interpreted as the ratio of the hazard functions for a one unit change in the variable, holding all other variables the same. The hazard function is the proportion of subjects who have an event (death) during a specified time period (i.e. chance of an event). It can be thought of conceptually as comparing the chance of an event (death) for two people with identical characteristics, except for the variable of interest for which they vary by only one unit. For variables that are categorical the comparison is made between

categories of the variable where one of the categories is the reference category against which the others are compared (i.e. hazard ratio of 1.0).

Disease stage, histologic grade, and the use of hormone therapy are predictive of breast cancer specific survival in women with LABC. Breast cancer specific mortality for women with disease stage 2B is 1.78 times that of women with stage 2A. Mortality continues to rise with increasing stage so that women with stage 3B disease will have mortality 4.72 times that of comparable women with stage 2A disease. An increase in breast cancer specific mortality is also seen with increasing histologic grade of the tumor, a women with a grade 3 tumor has a mortality 8.9 times that of a comparable women with a grade 1 tumor. The use of hormone therapy (estrogen inhibition) is associated with a decrease in mortality from breast cancer in the study patients (hazard ratio – 0.62). Breast cancer specific mortality was not affected by changes in the size of the tumor, age of the patient, or type of surgery used after adjusting for other variables (p-values > 0.05) (see Table 13).

The distinction between the use of neo-adjuvant chemotherapy and standard treatment is a key feature in the treatment of LABC. There is no significant difference in breast cancer specific survival between the two groups after adjusting for other factors (hazard ratio=1.24, p=0.466).

2. Testing the Assumptions of the Cox Model

An assumption of the Cox model is that of non-informative censoring. This refers to the design and collection of the data to ensure that no dropouts are related to the presence of the event [70]. For the current study, follow-up and outcome data are obtained through a linkage between Alberta Cancer Board data and Alberta Health Vital Statistics data and there is no reason to believe that a breast cancer death would change the reporting of such an event.

A major assumption of the Cox model is that of proportional hazards. This means that the hazard functions between any strata of explanatory variables are proportional; conceptually the plotted survival curves do not cross [74]. This assumption can be

tested using Schoenfeld residuals [74], and yields a p-value of 0.1904, which indicates an absence of evidence to contradict the assumption of proportionality. The proportional hazards assumption can also be tested graphically. If the curves in a plot of the Kaplan-Meier estimates and Cox predicted estimates for each explanatory variable are very close, then it is less likely the assumption is violated [70]. A log-log plot, plot of the natural log of the survival time versus the negative of the natural log of the negative of the natural log of survival (-ln(-ln(survival))) for each explanatory variable should produce parallel lines as evidence of the assumption of proportional hazards [74]. The Kaplan-Meier versus Cox plots for the study data shows that the predicted curves are very close to the Kaplan-Meier estimated curves (see Appendix A) suggesting the assumption holds. The log-log plots for the study data shows near parallel lines suggesting the assumption holds (see Appendix A).

The final set of assumptions about the Cox model is that of the linearity and additively of the linear predictor formula in the exponentiated form. The Cox model is based on a linear regression model of the hazard. Linear regression models use a mathematical equation with the following structure, which attempts to produce values which are close to ("fits") the existing data. The mathematical equation takes on the structure of:

$$b^T x_i = b_1 x_{1i} + b_2 x_{2i} + \ldots + b_p x_{pi}$$

Where b is the coefficient term at time interval t, x is the variable value for subject i at time t [70]. This equation will provide a mathematical prediction for the outcome variable for a person who has the characteristics defined by the group of explanatory variables (x1, x2,...,xi). The coefficients (b terms) are constants which try to adjust the result of the equation to come as close as possible to the "real" data. When we test how close the values that the equation predicts are to the actual data values, we are testing how good the model predicts or fits the real situation. When this test is done, we can calculate the difference between the predicted value and the real value for each group of "x's". This calculated difference is called the residual, the residual difference between the predicted and real value. If the model "fits" the data well, the residuals will be small; if the model is not so good, the residuals will be large. This mathematical formula assumes the relationship of one x variable to the next is additive and linear. For use in the Cox model, this equation is placed in the exponent

form to ensure a positive outcome value of the hazard function. To test the assumption of linearity and additivity the residual values can be plotted, and if they appear to show a relative horizontal pattern, it means there is not some systematic error (as represented by a curve or other pattern) that the model is making compared to the real data [74]. If there is a relative horizontal pattern to the plotted residuals, then the assumption of linearity and additivity of the explanatory variables in the exponentiated form can be accepted.

The plots of Martingale residuals versus the explanatory variables [74] show a relative horizontal pattern that supports the assumptions (see Appendix A - Regression Diagnostic Plots).

VI. Discussion: Survival Analysis

In Alberta during the period 1994-1996, 15% of breast cancer cases presented as locally advanced non-metastatic disease. The survival of breast cancer patients is related to the stage of presentation, and thus advanced disease has a poorer prognosis. 52% of patients presenting with LABC will die within 8 years, and almost 70% of those deaths will be caused by breast cancer. An increasing volume of literature suggests that patients presenting with tumors greater than 3 cm or fixed and bulky nodal disease should be treated with neo-adjuvant chemotherapy [19]. A look at our own local data suggests that only 15% of LABC patients are treated with neo-adjuvant chemotherapy. The crude survival of patients treated with neo-adjuvant chemotherapy versus standard therapy suggests that the patients receiving standard therapy have a survival benefit ($p=0.01$); this difference was not seen after adjusting for other factors. Patients who received neo-adjuvant chemotherapy tended to be younger ($p<0.001$), have larger tumors ($p<0.001$), and had greater proportions of higher TNM stages ($p<0.001$) (see Table 5). But, survival for women, after adjusting for other factors, was not different for younger patients or women with larger tumors. When the difference in TNM stage between the women treated with neo-adjuvant and standard therapy is considered (in the Cox model) there is no difference in survival. It is possible that patients were selected for neo-adjuvant chemotherapy because they

had factors which convey an increased risk (higher stage of disease). If patients are chosen for a particular treatment based on a factor which will affect survival, then the apparent difference in survival seen between treatments is not a result of the difference in treatment but a result of the groups being different, confounding by indication. There are other possible explanations for differences in survival between treatment groups in our retrospective data. Residual confounding, factors which we have not considered or measured that have an effect on survival, could be responsible for differences in survival between groups. Patients who have a contra-indication to one of the therapies will not be eligible for that treatment, and thus may not derive a possible benefit from that treatment. For example, a women who has a contra-indication against chemotherapy, co-morbid disease, would not be considered for neo-adjuvant chemotherapy and would by default be included in the standard therapy group. Using retrospective data can limit the conclusions reached when comparing two non-random groups.

Another of the treatment issues that was outlined in the background section is the most appropriate modality to be used after neo-adjuvant chemotherapy in patients who have a complete response in the tumor. Although no information is available in the current study population with respect to the level of response to neo-adjuvant chemotherapy, there is no difference in breast cancer specific survival between patients treated with surgery versus those treated with only radiation therapy after neo-adjuvant chemotherapy. Given that the groups are small, n=48 for surgery group and n=19 for radiation group, the results may be due to the small sample size or there may not be a difference in the two modalities in these patients. A larger study population of these patients with information on tumor response would be required to more adequately address this question.

The final therapeutic dilemma in the treatment of LABC is the issue of breast conserving therapies. It has been shown in a large randomized controlled trial of breast cancer patients that total mastectomy is equivalent to a segmental mastectomy with postoperative radiation therapy in terms of survival [73]. For some women the use of breast conservation therapies has a positive effect on their body image and may have a small impact on quality of life [75] [76]. The proportion of patients treated

with breast conserving therapies was significantly higher in the neo-adjuvant chemotherapy group (59%) versus the standard therapy group (30%) ($p<0.001$). This suggests that the larger tumors seen in the LABC population can be reduced in size by the use of neo-adjuvant chemotherapy, and make them more amenable to breast conservation therapies. Breast cancer specific survival of women treated with a mastectomy was equivalent to breast conserving therapy for both the standard therapy ($p=0.2595$) and neo-adjuvant chemotherapy ($p=0.2904$) groups.

Three variables have been identified which have prognostic value for women with LABC with regards to breast cancer specific survival. Those variables are the Stage of Disease, histopathologic grade of the tumor, and the use of hormone therapy. Stage of Disease would be expected to be a prognostic factor since it was developed to identify groups of patients with similar characteristics and prognosis to direct appropriate treatment and research. The hazard ratio increases with each step up in TNM stage, which suggests that survival decreases with each increase in stage.

The histopathologic grade of the tumor was also developed to identify pathologic characteristics that would group tumors with similar characteristics and women with similar prognosis. The group of LABC patients tend to have increased proportions of patients with higher grade tumors (47% are grade 3). This increased "aggressiveness" of tumors may account for why many patients still present with locally advanced disease; it is not due to a patient factor (denial, lack of care etc.) but may be a function of the tumor biology (more aggressive, faster growing etc.). The increased "aggressiveness" of the tumor may also result in a tumor that is more resistant to current treatments.

The use of hormone therapy was shown to be a significant predictor of breast cancer specific survival; patients who receive hormone therapy have a hazard function two thirds (0.64) that of patients not treated with hormone therapy. We need to remember that this is not randomized data and thus we may be measuring a direct or indirect effect of some other factor. Hormone therapy is usually given to patients that have tumors which contain estrogen hormone receptors on the cells. In the current study we are not able to say that hormone therapy is having a direct effect on survival or if

the reason (receptor status) that patients are given hormone therapy has an effect on survival (confounding by indication). Tumors that have estrogen receptors have a better prognosis even without hormone therapy; estrogen receptor status is an independent prognostic factor [71, 72, 77].

The study data suggests that age is not a significant predictor of breast cancer specific survival in women with LABC. This is similar to findings in other studies which suggest that younger patients tend to present with higher stage disease but stage for stage they appear to have similar survival [72]. Tumor size was also not found to be a significant predictor of breast cancer specific survival in the study population; there are a number of possible explanations for this. It is possible that other factors related to the tumor (such as grade) may be more important. Breast cancer specific survival may be more sensitive to the biology of the tumor, and not the size. It is also possible that once a tumor reaches 3 cm in size (defines LABC) further increases in size may not alter a women's survival, or other factors become more important for survival in this group.

VII. Conclusions: Survival Analysis

Breast cancer survival in LABC patients is related to disease stage, histological grade, and use of hormone therapy. No treatment modalities were predictive of survival. The difference in survival seen in women who were treated with hormone therapy may be the result of estrogen receptor status and not the hormone treatment itself. The use of neo-adjuvant chemotherapy did not appear to predict survival when other factors were considered. There was no difference in survival among patients treated with neo-adjuvant chemotherapy followed by either surgery or radiotherapy. Breast conserving techniques were used more frequently after neo-adjuvant chemotherapy than after standard therapy. There are no differences in survival for women treated with breast conserving therapies versus mastectomy.

VIII. Decision Analysis Framework Development

A. Specific Framework for Locally Advanced Breast Cancer Model

1. Decision Context and Perspective

The clinical problem of interest for the decision analysis methodology is treatment options for women with LABC. In order to frame the context of the problem a perspective must be defined. For the current decision model the perspective of the patients/physician will be used. Although other perspectives (institution or society) would be valid, an analysis of outcomes of importance to the individual patient may help guide important clinical study in the area of treatment of LABC. The target audience for the current project is patients with or at risk of LABC and their treating physicians. We have chosen this group as the primary target for the analysis because they represent an important starting point for consideration of treatment strategies. The issues the current study will address are how to use the currently available and accepted treatments to optimize the objectives of the patient.

2. Values, Objectives and Outcomes

With the problem and perspective defined, the values that underlie the decision context need to be framed. In the context of a condition that has the potential to limit lifespan of those affected, maximizing the lifespan of patients is an important value. Other values could be:

Returning to "healthy state" by tumor removal
Minimizing return of tumor
Maintaining current lifestyle
Not being sick
Minimize treatment impact on physical and mental appearance
Return to normal life as quickly as possible
Minimize pain
Minimize treatment side effects

The values listed above could be framed as fundamental objectives for the patient; these are the values that have intrinsic importance. This can be determined by asking

the question "why is this important?" for each value until the answer is that it is intrinsically important. All of the values identified can be distilled into two fundamental objectives. The first fundamental objective is the maximization of lifespan, because there is intrinsic value in living the longest period of time possible. The second fundamental objective is to maximize the quality of life that remains; there is intrinsic value in the highest quality of life. Quality of life includes the physical functioning, social functioning, and the mental/psychological functioning of a patient.

The impact of any alternative in the decision model needs to be measured in terms of these two objectives. The objective of lifespan will be measured as a function of the time from diagnosis to death. The objective of quality of life will be measured as quality of life weights based on the patient's health state at different points in time.

Once the fundamental objectives have been identified, the outcomes that are relevant to the decision context can be translated in terms of the fundamental objectives. The fundamental objective of survival can be translated into the outcomes of alive and dead. The second fundamental outcome, quality of life, is more complex as it encompasses not only aspects of one's health but also elements of physical, mental, and social functioning. There are a number of important outcomes from the treatment of LABC which could have a major impact on quality of life:

- the physical, mental and social impact of the treatment itself
- the physical, mental and social impact of a complication/side-effect from the treatment
- the physical, mental and social impact of a local recurrence of disease
- the physical, mental and social impact of a metastatic recurrence of disease

Recurrence in breast cancer refers to the development of tumor growth at either the site of the original tumor, draining lymph nodes of the original tumor, or at distant metastatic sites (unrelated tissue sites) (e.g. liver, lung, bone, brain). Because these issues will likely have profound impacts on quality of life they need to be included as potential outcomes from any of the treatment alternatives.

3. Alternatives and Model Structure

The next step is to list all possible alternatives for the decision context. For the case of treatment for LABC there are a number of potential treatment strategies based on the different combinations of the primary modalities, surgery (mastectomy or segmental mastectomy), radiation therapy, chemotherapy, and hormone therapy. Potentially, any combination of these modalities could be selected but there are some practical treatment considerations. Use of the drug tamoxifen will be the only hormone therapy considered in this model because it is considered a first line agent and there is significant data available regarding outcomes of its use. Hormone therapy is usually given for a prolonged period of time (years) and thus it is not likely to matter whether it is started before or after other treatments that only last for a much shorter period (days to weeks). It would be standard of care to administer post-operative radiation therapy to any patient who received a segmental mastectomy, and any patient who wishes not to have or is not a candidate for radiation therapy would only be offered a total mastectomy. If chemotherapy is given prior to other treatments, more chemotherapy is given after the other treatments. Radiation therapy is not given to patients who have had a mastectomy unless some unusual circumstances exist (e.g. microscopic tumor is identified on the margin of the surgical specimen). Given the practicalities the following is a list of potential treatment alternatives:

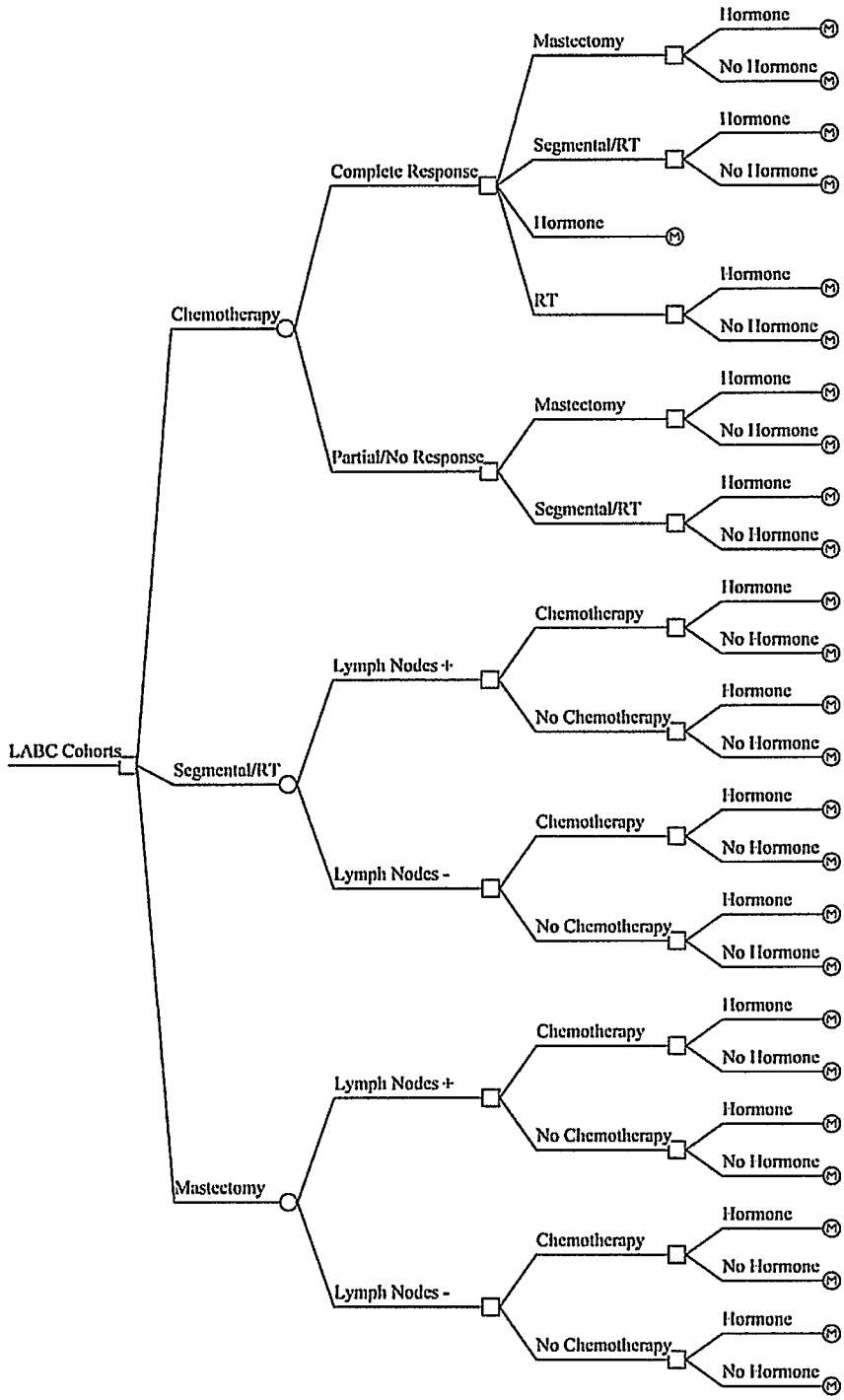
1. None - no treatment
2. Mastectomy
3. Segmental mastectomy + radiation therapy
4. Radiation therapy
5. Chemotherapy
6. Hormone therapy
7. Neo-Adjuvant chemotherapy + mastectomy + chemotherapy + or - Hormone therapy
8. Neo-Adjuvant chemotherapy + segmental mastectomy + radiation therapy + chemotherapy + or - Hormone therapy
9. Neo-Adjuvant chemotherapy + radiation therapy + chemotherapy + or - Hormone therapy
10. Mastectomy + Hormone therapy

11. Mastectomy + chemotherapy + or - Hormone therapy
12. Segmental mastectomy + radiation therapy + Hormone therapy
13. Segmental mastectomy + radiation therapy + chemotherapy + or - Hormone therapy

It should be recognized that alternatives # 1 - 6 would not be routinely recommended and would fall outside the normal practice patterns for a normal distribution of LABC patients. Although these options do exist, they will not be included in the decision model because they would only be used in rare and unusual situations.

The idealized model for the decision analysis can be seen in Figure 18. It represents the general tree structure with events moving from the left to the right. It begins with the selection of a cohort of patients, because there are survival differences for different AJCC TNM stages, menopausal status (pre and post), and estrogen receptor status [19] [71], each of these cohorts will be evaluated in the decision analysis separately. A total of 16 different cohorts will be analyzed to account for the different combinations of the TNM stages for LABC, pre- and post-menopausal groups and receptor positive and negative tumors (see Table 14).

Figure 18 - Decision Tree for the Treatment of Patients with LABC



Data 3.5, TreeAge Software

Table 14 – Listing of the 16 Different Cohorts by TNM Stage, Menopausal Status, and Estrogen Receptor Status that will be used in the Decision Analysis for LABC

Cohort	*TNM Stage*	*Menopausal Status*	*Estrogen Receptor Status*
1	2A	Pre-Menopausal	Negative
2	2A	Pre-Menopausal	Positive
3	2A	Post-Menopausal	Negative
4	2A	Post-Menopausal	Positive
5	2B	Pre-Menopausal	Negative
6	2B	Pre-Menopausal	Positive
7	2B	Post-Menopausal	Negative
8	2B	Post-Menopausal	Positive
9	3A	Pre-Menopausal	Negative
10	3A	Pre-Menopausal	Positive
11	3A	Post-Menopausal	Negative
12	3A	Post-Menopausal	Positive
13	3B	Pre-Menopausal	Negative
14	3B	Pre-Menopausal	Positive
15	3B	Post-Menopausal	Negative
16	3B	Post-Menopausal	Positive

After the diagnosis of locally advanced invasive breast carcinoma, the first decision node allows one to make the choice of initial treatment between neo-adjuvant chemotherapy, mastectomy or segmental mastectomy with post-operative radiation therapy. If we follow the path along the choice of neo-adjuvant chemotherapy (chemotherapy as the initial treatment) a chance node exists which reflects the response of the primary tumor to the chemotherapy. A complete response would be defined as a tumor that is clinically and radiographically non-detectable, and multiple core or needle biopsies of the previous tumor area are negative for cancer. A partial response would be defined as a tumor that has decreased in size, clinically and/or radiographically, but is still detectable. A no-response would be defined as a tumor

that stayed the same or increased in size after treatment with chemotherapy. After assessment of the response rate, a decision node represents the next therapeutic step. For complete responders, the choice is between mastectomy, segmental mastectomy with post-operative radiation therapy, radiation therapy, or hormone therapy. For partial or non-responders, the choice is between the two surgical options of mastectomy or segmental mastectomy with post-op radiation therapy. It is assumed that all patients will be offered follow-up completion chemotherapy. A decision node for the use of hormone therapy follows.

The other branches of the tree begin with the choice of a surgical option as the initial treatment. Segmental resection and post-operative radiation therapy is followed by a chance node grouping tumors based on the lymph node status. This is an important distinction because the decision node that follows is a choice between the use or not of chemotherapy. The trade-off of the risk of side-effects and complications versus potential benefit in survival is different for the two groups. Again there is a choice between hormone and no hormone therapy. The final branch of the decision tree represents the initial choice of mastectomy. The branches after mastectomy mirror that of the segmental resection branch as discussed above.

At the completion of each different treatment algorithm, a Markov subtree is used to model the various outcomes, as described below.

4. Time and its incorporation into the model

Markov modelling will be well suited to be included in the analysis of treatment options in LABC. The use of a standard tree structure and finite time horizon would fail to capture the true nature of the long-term outcomes. Survival in breast cancer should be best described in terms of at least 10-year survival [19], and more appropriately a lifetime. If a Markov process is not used, the changing probabilities of recurrence and death over time could not be included. Also, it would fail to demonstrate how utilities might vary over time as a result of movement through different stages of disease progression and treatment.

In this analysis, there are four general health states that should be included as outcomes/health states related to LABC in the Markov process are:

Disease Free – is a patient who is alive and has no clinical evidence of breast cancer.

Local Recurrence – is a patient who is alive and has clinical and pathologic evidence for breast cancer located in the surgical field (mastectomy) or same quadrant of the breast (segmental resection or radiation therapy) and/or in the axillary tissue on the same side as the previous cancer.

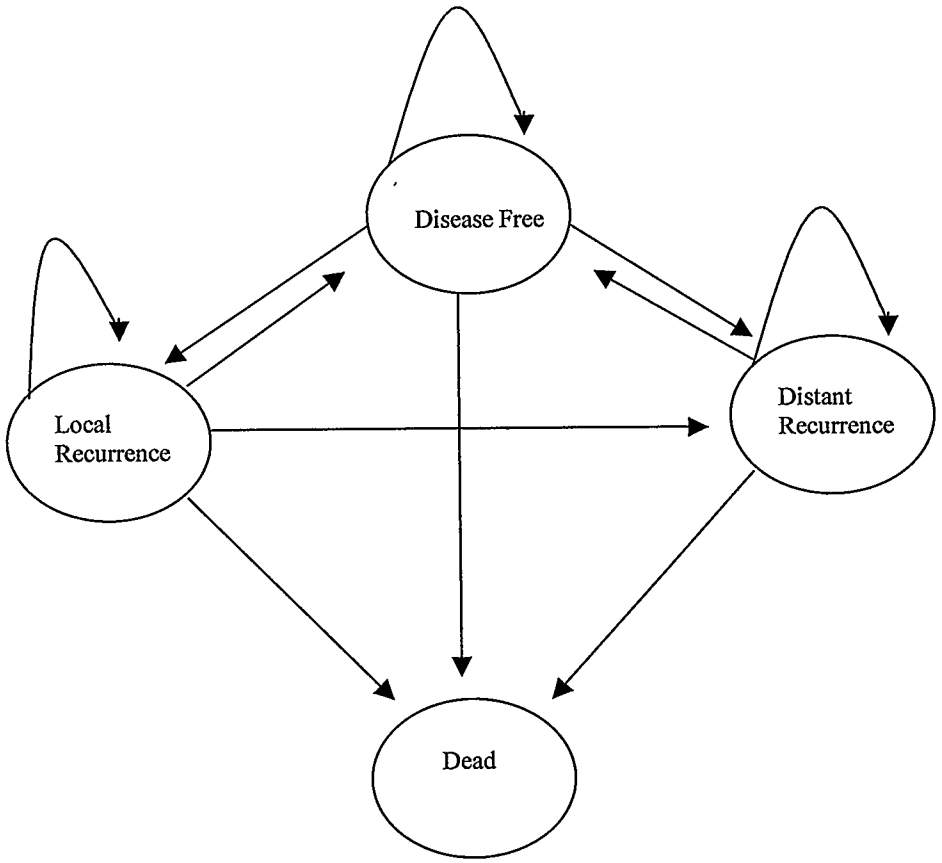
Distant Recurrence – is a patient who is alive and has clinical or radiological and pathological evidence for breast cancer at a site distant to the original tumor, i.e. metastatic disease.

Dead - is a patient who has died

The allowed transitions between health states can be diagrammed as shown in Figure 19. Each arrow (transition) will be associated with a transition probability. Each unique health state will be associated with a utility value, represented by QALYs.

The cycle length will be set at one year. This represents a clinically appropriate time interval because the events we are examining occur over a relatively long period of time and clinically important transitions in health status will occur during intervals of about one year.

Figure 19 - Markov Health States and Allowed Transitions Between States for the Decision Analysis Model of Women with LABC



5. Treatment Complications

Each specific treatment modality used in the treatment of breast cancer has specific complications associated with it. Many, if not all, of these treatment complications can result in a change in the patient's quality of life. It will be important to incorporate these changes in quality of life into the model through the introduction of a more complex Markov model, with each complication being represented as a separate health state with its own associated utility weighting and transition probabilities. An initial assumption could be made that the development of a recurrence of disease either locally or distant would be a much more important issue so patients would move to these health states without continued consideration of the impact of treatment complications; however, assessment of complications may be informative in a revised analysis.

The following is a list of some possible treatment complications for each modality:

- Surgery
  - Pain (chronic)
  - Physical disfigurement or body image change
  - Lymphatic obstruction
  - Medical complications (Blood clots, myocardial infarction, stroke)
- Chemotherapy
  - Bone marrow suppression
  - Infection
  - Hair loss or other body image change
- Radiation Therapy
  - Wound/Skin breakdown
  - Physical disfigurement
  - Lung injury
  - Lymphatic obstruction
- Hormone (Tamoxifen) Therapy [78]
  - Hot flashes
  - Endometrial cancer
  - Stroke
  - Deep venous thrombosis (blood clot)

Pulmonary embolism (blood clot to the lungs)

Cataracts

6. Probabilities and Utility Values

This represents the data synthesis portion of the decision analysis. The probabilities associated with the outcomes of chance nodes in the decision tree and transition probabilities for the Markov process as well as the utility values associated with each treatment alternative and utility values associated with each Markov health state need to be defined. This process should begin with a detailed statement regarding each probability and utility required so that the exact context for each is defined. Once each probability and utility has been defined, values for each are identified. The process for identifying the values, as discussed previously, uses the hierarchy of evidence beginning with published literature and a structured literature search. If information cannot be found in the literature then, if applicable, a review of existing databases will be performed or subjective probabilities from expert or personal opinion will be used. In order to elicit probability values from experts a defined group of individuals who have an expertise in the area of interest needs to be formed. Once a group is available, the process of determining a value will begin with each member submitting their estimate. The group of estimates are then anonymously presented back to the group for discussion and clarification of the estimate. An estimate of the uncertainty of this parameter can be estimated based on the spread or distribution of the estimates given by different groups or individuals. For parameters which relate to elements of utility, for which there are no estimates in the literature, a similar group method can be used for estimation. The members of the "expert group" would be gathered from current or former women with the condition, members of the general public, and nursing staff experienced in treating women with the condition. These "experts" will be able to give a real world and educated estimate of the impact of the condition on quality of life.

The identification of utility values for the LABC model will be selected by a review of the available databases of published utility values: Bell et al. [64], Tengs and Wallace [61], Beaver Dam Health Outcomes Study [62], National Health Interview Survey [63], and a computerized literature search for relevant published articles not

identified in the databases. An assumption is made that it does not matter how one gets to a health state (which treatment strategy), the utility associated with the state are the same. The exception to this is the state of Disease Free, which will have a utility value specific for each treatment strategy. Each individual treatment regimen is associated with a decrease in quality of life based on the unpleasantness of the treatment, time costs, and short-term common side effects of the treatment. This will be modeled by utilizing a utility factor for the health state Disease Free for the first cycle for each specific treatment regimen. This quality of life value will account for the difference in the "unpleasantness" of different treatment programs in the decision tree. The utility value of this state in the subsequent cycles will then be based on a more general quality of life experienced after the specific treatment regimen.

The following is a list of the probabilities and utilities required for the analysis. A separate value will be required for each probability and utility for all of the initial 16 cohorts. The transition probabilities will need to be specific for each cohort and for each treatment strategy used; and these transition probabilities may vary and change over time.

Probabilities:

a. complete response to neo-adjuvant chemotherapy
b. partial or no response to neo-adjuvant chemotherapy
c. positive lymph nodes after surgery (this will be the same probability after either mastectomy or segmental mastectomy)
d. negative lymph nodes after surgery (this will be the same probability after either mastectomy or segmental mastectomy)

Transition Probabilities:

1. Disease Free to Same State
2. Disease Free to Local Recurrence
3. Disease Free to Distant Recurrence
4. Disease Free to Dead
5. Local Recurrence to Same State
6. Local Recurrence to Disease Free
7. Local Recurrence to Distant Recurrence
8. Local Recurrence to Dead

9. Distant Recurrence to Same State
10. Distant Recurrence to Dead

Utilities:

a. Disease Free State - this utility value will be different for each of the different treatment strategies identified in the decision tree.
b. Local Recurrence State
c. Distant Recurrence State
d. Dead State

7. Stopping Rules

The analysis will be run for 25 cycles (years). This will provide a reasonable estimate over the predicted lifespan of the average LABC patient. It also has validity with regards to the risk period for recurrence of disease.

8. Sensitivity Analysis

A combination of sensitivity analysis methods will be utilized for the LABC model described. The initial step in this portion of the analysis will use a deterministic approach by applying a one-way analysis based on the range of values for uncertainty identified for each probability, utility, and transition probability in the model. This will provide us with some basic information on the nature of the variables upon which the analysis is sensitive. A "best case" and "worst case" scenario will then be utilized by running the analysis with values for the probabilities and utilities that represent the best and worst cases. The results of the best/worst cases will provide information about which alternatives are preferred under the most extreme conditions. A best case would utilize probabilities which would yield the most optimistic values for survival, and utilities which would yield the most optimistic values for quality of life. A worst case would provide the opposite assessment, using the least optimistic probabilities and utilities.

The next step in the sensitivity analysis will be to utilize a probabilistic approach to the parameter uncertainty. For each variable of probability and utility, a probability distribution that represents the variability in that variable will be created. This process will require that information from the literature or experts be elicited

regarding the choice of a distribution for each variable that seems most appropriate. Once the distributions for each variable have been determined, a Monte-Carlo simulation method will be used and run many (n=5000) times. The simulation run over a large number of times will be required to provide a useful estimate of the outcome because there are many parameters (probabilities and utilities) each with their own distribution for which only one value can be used in any single run. The simulation run over a large number of times will allow for parameter values within each probability to be used, as well as the combinations of different parameter values. A large number of simulations will also be required to provide estimates of outcome for which there may be only small differences between groups.

The sensitivity analysis will likely result in the identification of parameters used in the model to which the choice of the preferred alternative is sensitive. The identification of these parameters will allow for more work to be done to either provide more accurate estimates for the parameter or provide insight into the important factors for patients faced with decisions about the treatment of LABC.

B. The Next Step

The framework for a decision analysis model has been described. Referring back to the flowchart for the process (see Figure 2), the next step would be to begin data collection. This will provide the estimates for all required parameters set out in the framework. These estimates are then fit into the model and the simulation is done. A sensitivity analysis, as described, would then be performed leading to an analysis of the ranking of treatment alternatives and insight into variables to which the analysis is sensitive. Interpretation of the model at this point may lead back to refinement of the model and estimates, or it may lead to conclusions which can be interpreted within the context of the decision problem.

C. The Benefit of a Decision Analysis

The information extracted from the literature and the survival analysis provided in the current study suggest that there are a number of treatment options for women with LABC, but all treatment options are similar in terms of breast cancer specific survival. If all treatment options appear equal in terms of survival then how do we advise patients regarding which treatment to choose? As identified in the discussion of the objectives section of the decision analysis, there are other values and objectives which are important to breast cancer patients. These other objectives will be important to consider when treatment decisions are to be made. One of the fundamental objectives identified is quality of life during and after treatment. The benefit of the information gained from the decision analysis is that information regarding both length and quality of life can be examined for the various treatment options. By including information about quality of life differences between treatment options the decision process can be expanded to include these other important objectives. The decision analysis can provide information about quality of life differences among different treatment options which may give patients insight into these decisions. The integration of the evidence of treatment effectiveness (survival) and patient values (quality of life) is an advantage of providing the decision analysis for women with LABC to help advise treatment decisions.

References:

1. CCS, *Canadian Cancer Society, Canadian breast cancer statistics.* www.cancer.ca/ccs, 2002.
2. Esteva, F.J. and G.N. Hortobagyi, *Locally advanced breast cancer.* Hematol Oncol Clin North Am, 1999. **13**(2): p. 457-72, vii.
3. Valero, V.V., A.U. Buzdar, and G.N. Hortobagyi, *Locally Advanced Breast Cancer.* Oncologist, 1996. **1**(1): p. 8-17.
4. Calais, G., et al., *Conservative treatment feasibility with induction chemotherapy, surgery, and radiotherapy for patients with breast carcinoma larger than 3 cm.* Cancer, 1994. **74**(4): p. 1283-8.
5. Bonadonna, G., et al., *Primary chemotherapy to avoid mastectomy in tumors with diameters of three centimeters or more.* J Natl Cancer Inst, 1990. **82**(19): p. 1539-45.
6. Bonadonna, G., et al., *Primary chemotherapy in operable breast cancer: eight-year experience at the Milan Cancer Institute.* J Clin Oncol, 1998. **16**(1): p. 93-100.
7. Belembaogo, E., et al., *Neoadjuvant chemotherapy in 126 operable breast cancers.* Eur J Cancer, 1992: p. 896-900.
8. Kuerer, H.M., et al., *Residual metastatic axillary lymph nodes following neoadjuvant chemotherapy predict disease-free survival in patients with locally advanced breast cancer.* Am J Surg, 1998. **176**(6): p. 502-9.
9. Kuerer, H.M., et al., *Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy.* J Clin Oncol, 1999. **17**(2): p. 460-9.
10. Makris, A., et al., *A reduction in the requirements for mastectomy in a randomized trial of neoadjuvant chemoendocrine therapy in primary breast cancer.* Ann Oncol, 1998. **9**(11): p. 1179-84.
11. Mauriac, L., et al., *Effects of primary chemotherapy in conservative treatment of breast cancer patients with operable tumors larger than 3 cm. Results of a randomized trial in a single centre.* Ann Oncol, 1991. **2**(5): p. 347-54.
12. Powles, T.J., et al., *Randomized trial of chemoendocrine therapy started before or after surgery for treatment of primary breast cancer.* J Clin Oncol, 1995. **13**(3): p. 547-52.

13. Scholl, S.M., et al., *Neoadjuvant versus adjuvant chemotherapy in premenopausal patients with tumours considered too large for breast conserving surgery: preliminary results of a randomised trial: S6.* Eur J Cancer, 1994. **5**: p. 645-52.

14. Schwartz, G.F., et al., *Induction chemotherapy followed by breast conservation for locally advanced carcinoma of the breast.* Cancer, 1994. **73**(2): p. 362-9.

15. Semiglazov, V.F., et al., *Primary (neoadjuvant) chemotherapy and radiotherapy compared with primary radiotherapy alone in stage IIb-IIIa breast cancer.* Ann Oncol, 1994. **5**(7): p. 591-5.

16. Smith, I.E., et al., *High complete remission rates with primary neoadjuvant infusional chemotherapy for large early breast cancer.* J Clin Oncol, 1995. **13**(2): p. 424-9.

17. Haagensen, C.D., A.P. Stout, *Carcinoma of the breast: II. Criteria of Operability.* Annals of Surgery, 1943. **118**: p. 859-1032.

18. Halsted, W.S., *The results of radical operations for the cure of carcinoma of the breast.* Annals of Surgery, 1907. **56**: p. 1 -19.

19. Berger, D.H., B.W. Feig, and G.M. Fuhrman, *The M.D. Anderson surgical oncology handbook.* 1st ed. 1995, Boston: Little Brown. xvi, 440.

20. Schottenfeld, D., et al., *Ten-year results of the treatment of primary operable breast carcinoma: A summary of 304 patients evaluated by the TNM system.* Cancer, 1976. **38**(2): p. 1001-7.

21. Arnold, D.J. and G.J. Lesnick, *Survival following mastectomy for stage III breast cancer.* Am J Surg, 1979. **137**(3): p. 362-6.

22. Fracchia, A.A., J.F. Evans, and B.L. Eisenberg, *Stage III carcinoma of the breast. A detailed analysis.* Ann Surg, 1980. **192**(6): p. 705-10.

23. Bland, K.I. and E.M. Copeland, *The breast : comprehensive management of benign and malignant diseases.* 2nd ed. 1998, Philadelphia ; Toronto: W.B. Saunders. 2 v. (xxxiv, 1631).

24. Harris, J.R., et al., *Management of locally advanced carcinoma of the breast by primary radiation therapy.* Int J Radiat Oncol Biol Phys, 1983. **9**(3): p. 345-9.

25. Zucali, R., et al., *Natural history and survival of inoperable breast cancer treated with radiotherapy and radiotherapy followed by radical mastectomy.* Cancer, 1976. **37**(3): p. 1422-31.

26. Grohn, P., et al., *Adjuvant postoperative radiotherapy, chemotherapy, and immunotherapy in stage III breast cancer.* Cancer, 1984. **54**(4): p. 670-4.

27. Klefstrom, P., et al., *Adjuvant postoperative radiotherapy, chemotherapy, and immunotherapy in stage III breast cancer. II. 5-year results and influence of levamisole.* Cancer, 1987. **60**(5): p. 936-42.

28. Schaake-Koning, C., et al., *Adjuvant chemo- and hormonal therapy in locally advanced breast cancer: a randomized clinical study.* Int J Radiat Oncol Biol Phys, 1985. **11**(10): p. 1759-63.

29. Rubens, R.D., et al., *Locally advanced breast cancer: the contribution of cytotoxic and endocrine treatment to radiotherapy. An EORTC Breast Cancer Co- operative Group Trial (10792).* Eur J Cancer Clin Oncol, 1989. **25**(4): p. 667-78.

30. Derman, D.P., et al., *Adjuvant chemotherapy (CMF) for stage III breast cancer: a randomized trial.* Int J Radiat Oncol Biol Phys, 1989. **17**(2): p. 257-61.

31. Fisher, B., et al., *Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18.* J Clin Oncol, 1997. **15**(7): p. 2483-93.

32. Fisher, B., et al., *Effect of preoperative chemotherapy on the outcome of women with operable breast cancer.* J Clin Oncol, 1998. **16**(8): p. 2672-85.

33. Buzdar, A.U., et al., *Combined modality treatment of stage III and inflammatory breast cancer. M.D. Anderson Cancer Center experience.* Surg Oncol Clin N Am, 1995. **4**(4): p. 715-34.

34. Sorace, R.A., et al., *The management of nonmetastatic locally advanced breast cancer using primary induction chemotherapy with hormonal synchronization followed by radiation therapy with or without debulking surgery.* World J Surg, 1985. **9**(5): p. 775-85.

35. Swain, S.M., et al., *Neoadjuvant chemotherapy in the combined modality approach of locally advanced nonmetastatic breast cancer.* Cancer Res, 1987. **47**(14): p. 3889-94.

36. Anderson, E.D., et al., *Primary systemic therapy for operable breast cancer.* Br J Cancer, 1991. **63**(4): p. 561-6.

37. Conte, P.F., et al., *Chemotherapy with estrogenic recruitment and surgery in locally advanced breast cancer: clinical and cytokinetic results.* Int J Cancer, 1987. **40**(4): p. 490-4.

38. Hobar, P.C., et al., *Multimodality treatment of locally advanced breast carcinoma.* Arch Surg, 1988. **123**(8): p. 951-5.

39. Piccart, M.J., et al., *Six-year results of a multimodality treatment strategy for locally advanced breast cancer.* Cancer, 1988. **62**(12): p. 2501-6.

40. Jacquillat, C., et al., *Results of neoadjuvant chemotherapy and radiation therapy in the breast- conserving treatment of 250 patients with all stages of infiltrative breast cancer.* Cancer, 1990. **66**(1): p. 119-29.

41. Calais, G., et al., *Primary chemotherapy and radiosurgical breast-conserving treatment for patients with locally advanced operable breast cancers.* Int J Radiat Oncol Biol Phys, 1993. **26**(1): p. 37-42.

42. Hortobagyi, G.N., et al., *Management of stage III primary breast cancer with primary chemotherapy, surgery, and radiation therapy.* Cancer, 1988. **62**(12): p. 2507-16.

43. Ragaz, J., *Emerging modalities for adjuvant therapy of breast cancer: neoadjuvant chemotherapy.* NCI Monogr, 1986. **1**: p. 145-52.

44. Ragaz, J., et al., *Neoadjuvant (preoperative) chemotherapy for breast cancer.* Cancer, 1985. **56**(4): p. 719-24.

45. Goldie, J.H. and A.J. Coldman, *A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate.* Cancer Treat Rep, 1979. **63**(11-12): p. 1727-33.

46. Skipper, H.E., *Kinetics of mammary tumor cell growth and implications for therapy.* Cancer, 1971. **28**(6): p. 1479-99.

47. Gunduz, N., B. Fisher, and E.A. Saffer, *Effect of surgical removal on the growth and kinetics of residual tumor.* Cancer Res, 1979. **39**(10): p. 3861-5.

48. Fisher, B., N. Gunduz, and E.A. Saffer, *Influence of the interval between primary tumor removal and chemotherapy on kinetics and growth of metastases.* Cancer Res, 1983. **43**(4): p. 1488-92.

49. Simpson-Herren, L., A.H. Sanford, and J.P. Holmquist, *Effects of surgery on the cell kinetics of residual tumor.* Cancer Treat Rep, 1976. **60**(12): p. 1749-60.

50. Perloff, M., et al., *Combination chemotherapy with mastectomy or radiotherapy for stage III breast carcinoma: a Cancer and Leukemia Group B study.* J Clin Oncol, 1988. **6**(2): p. 261-9.

51. De Lena, M., et al., *Multimodal treatment for locally advanced breast cancer. Result of chemotherapy-radiotherapy versus chemotherapy-surgery.* Cancer Clin Trials, 1981. **4**(3): p. 229-36.

52. Cocconi, G., et al., *Neoadjuvant chemotherapy or chemotherapy and endocrine therapy in locally advanced breast carcinoma. A prospective, randomized study.* Am J Clin Oncol, 1990. **13**(3): p. 226-32.

53. Singletary, S.E., M.D. McNeese, and G.N. Hortobagyi, *Feasibility of breast-conservation surgery after induction chemotherapy for locally advanced breast carcinoma.* Cancer, 1992. **69**(11): p. 2849-52.

54. Pierce, L.J., et al., *The effect of systemic therapy on local-regional control in locally advanced breast cancer.* Int J Radiat Oncol Biol Phys, 1992. **23**(5): p. 949-60.

55. Bonadonna, G., et al., *Primary chemotherapy in surgically resectable breast cancer.* CA Cancer J Clin, 1995. **45**(4): p. 227-43.

56. Hunink, M.G.M., *Decision making in health and medicine : integrating evidence and values*. 2001, Cambridge ; New York, NY: Cambridge University Press. xvi, 388.

57. Naimark, D., et al., *Primer on medical decision analysis: Part 5--Working with Markov processes.* Med Decis Making, 1997. **17**(2): p. 152-9.

58. Clemen, R.T., *Making hard decisions : an introduction to decision analysis*. 2nd ed. 1996, Belmont, Calif.: Duxbury Press. xxiv, 664.

59. Von Neumann, J. and O. Morgenstern, *Theory of games and economic behavior*. [2d] ed. 1947, Princeton: Princeton University Press. xviii, 641.

60. Keeney, R.L., *Value-focused thinking : a path to creative decisionmaking.* 1992, Cambridge, Mass.: Harvard University Press. xvi, 416.

61. Tengs, T.O. and A. Wallace, *One thousand health-related quality-of-life estimates.* Med Care, 2000. **38**(6): p. 583-637.

62. Fryback, D.G., et al., *Predicting Quality of Well-being scores from the SF-36: results from the Beaver Dam Health Outcomes Study.* Med Decis Making, 1997. **17**(1): p. 1-9.

63. Gold, M.R., et al., *Toward consistency in cost-utility analyses: using national measures to create condition-specific values.* Med Care, 1998. **36**(6): p. 778-92.

64. Bell, C.M., et al., *An off-the-shelf help list: a comprehensive catalog of preference scores from published cost-utility analyses.* Med Decis Making, 2001. **21**(4): p. 288-94.

65. Weinstein, M.C. and H.V. Fineberg, *Clinical decision analysis.* 1980, Philadelphia: Saunders. xiv, 351.

66. Detsky, A.S., et al., *Primer on medical decision analysis: Part 1--Getting started.* Med Decis Making, 1997. **17**(2): p. 123-5.

67. Naglie, G., et al., *Primer on medical decision analysis: Part 3--Estimating probabilities and utilities.* Med Decis Making, 1997. **17**(2): p. 136-41.

68. Sonnenberg, F.A. and J.R. Beck, *Markov models in medical decision making: a practical guide.* Med Decis Making, 1993. **13**(4): p. 322-38.

69. Krahn, M.D., et al., *Primer on medical decision analysis: Part 4--Analyzing the model and interpreting the results.* Med Decis Making, 1997. **17**(2): p. 142-51.

70. Lee, E.T. and O.T. Go, *Survival analysis in public health research.* Annu Rev Public Health, 1997. **18**: p. 105-34.

71. Kaufmann, M., *Review of known prognostic variables.* Recent Results Cancer Res, 1996. **140**: p. 77-87.

72. Masood, S., *Prediction of recurrence for advanced breast cancer. Traditional and contemporary pathologic and molecular markers.* Surg Oncol Clin N Am, 1995. **4**(4): p. 601-32.

73. Fisher, B., et al., *Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer.* N Engl J Med, 2002. **347**(16): p. 1233-41.

74. Brant, R., *Cox Proportional Hazards Model and Assumptions.* MDSC 643.02: Biostatistics II Personal Communication and Class Notes, 2001. **Chapt 4.3 - 4.5.**

75. Janni, W., et al., *Quality of life influenced by primary surgical treatment for stage I- III breast cancer-long-term follow-up of a matched-pair analysis.* Ann Surg Oncol, 2001. **8**(6): p. 542-8.

76. Irwig, L. and A. Bennetts, *Quality of life after breast conservation or mastectomy: a systematic review.* Aust N Z J Surg, 1997. **67**(11): p. 750-4.

77. Valavaara, R., *Reliability of estrogen receptors in predicting response to antiestrogens.* Oncology (Huntingt), 1997. **11**(5 Suppl 4): p. 14-8.

78. Fisher, B., et al., *Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study.* J Natl Cancer Inst, 1998. **90**(18): p. 1371-88.

Appendix A – Cox Proportional Hazards Diagnostic Plots

Figure 1 - Kaplan-Meier estimates versus Cox predicted estimates for disease stage

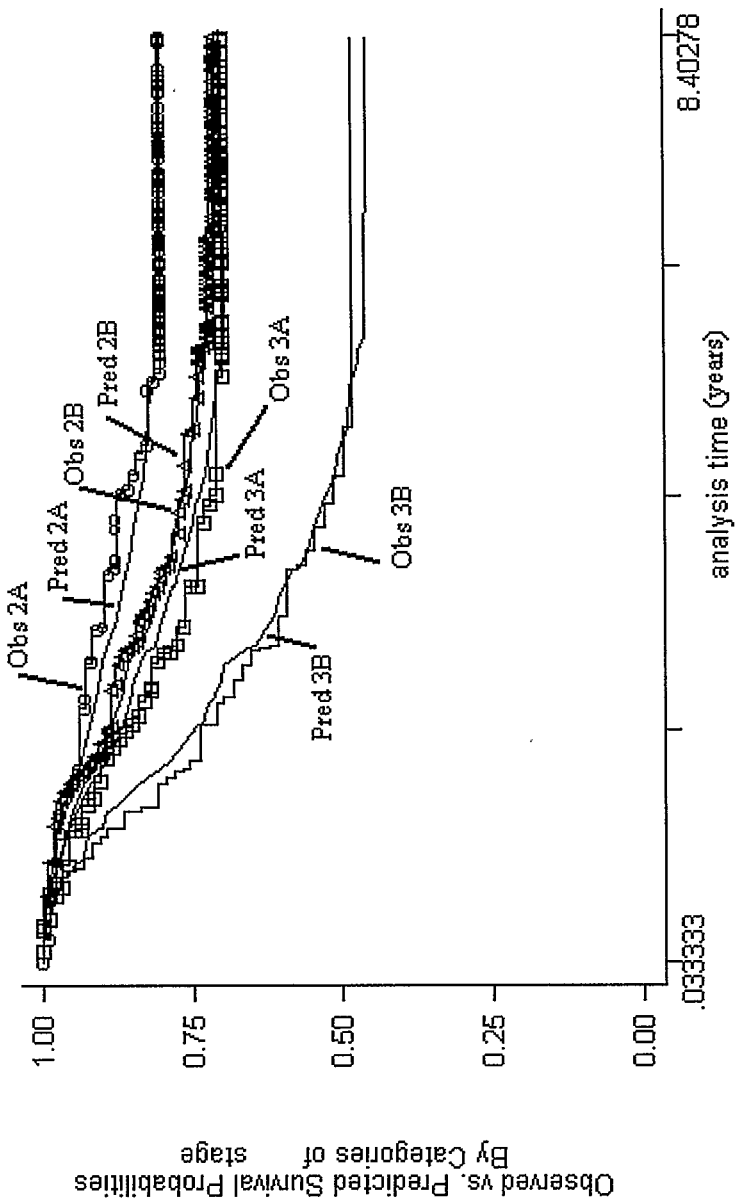


Figure 2 - Kaplan-Meier estimates versus Cox predicted estimates for Histologic Grade

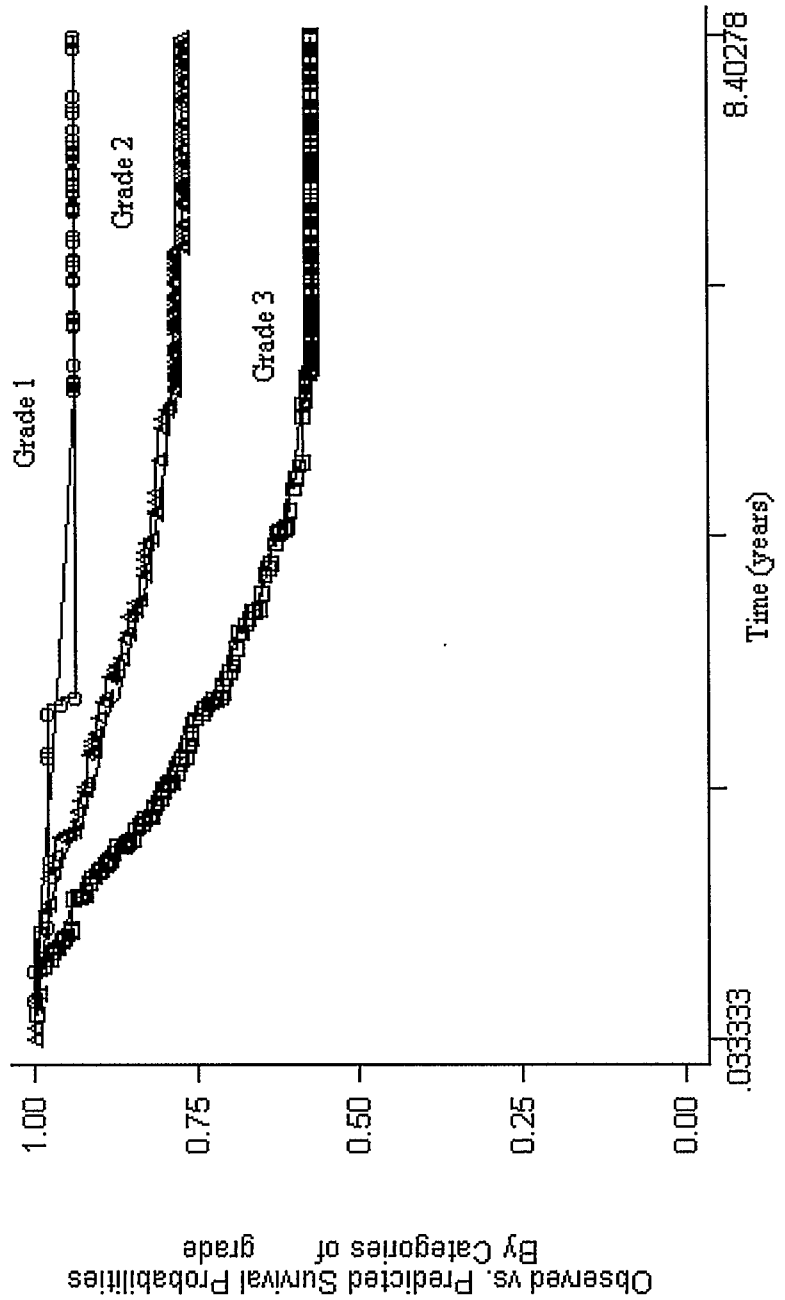


Figure 3 - Kaplan-Meier estimates versus Cox predicted estimates for Hormone therapy

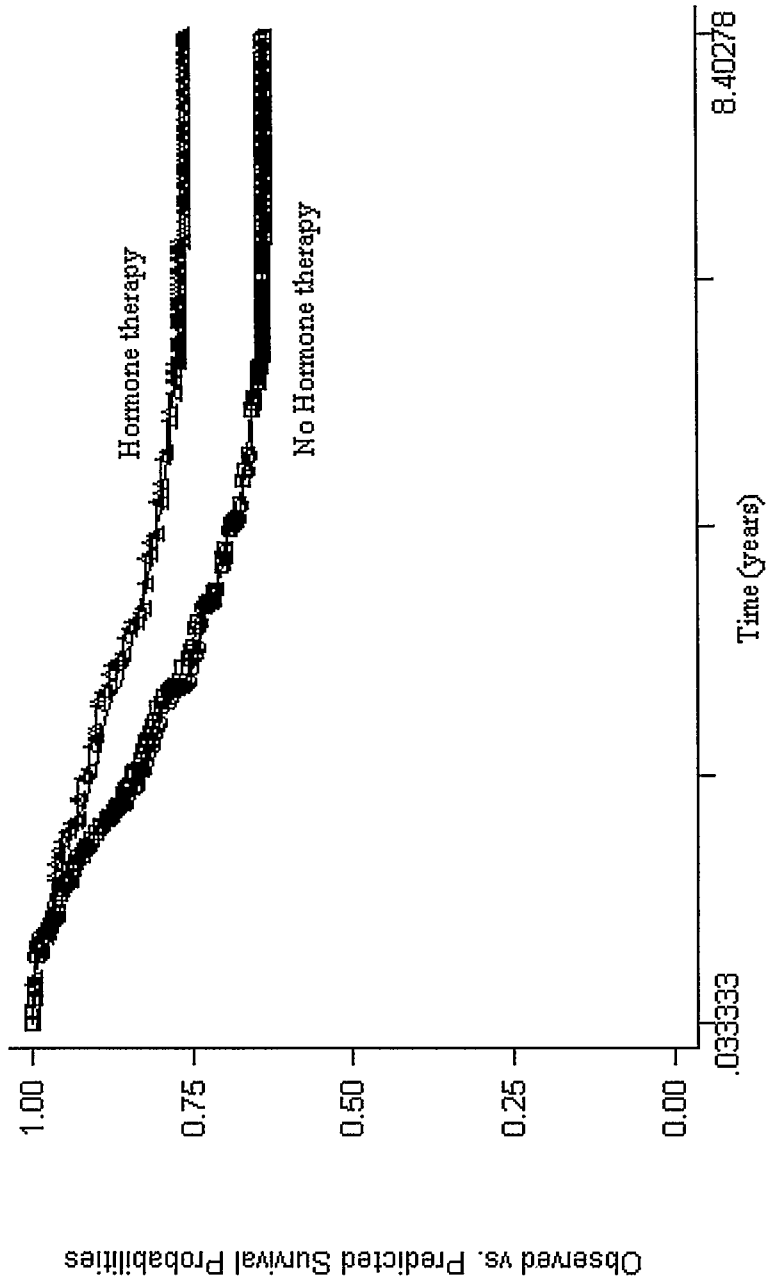


Figure 4 - Kaplan-Meier estimates versus Cox predicted estimates for Treatment Type

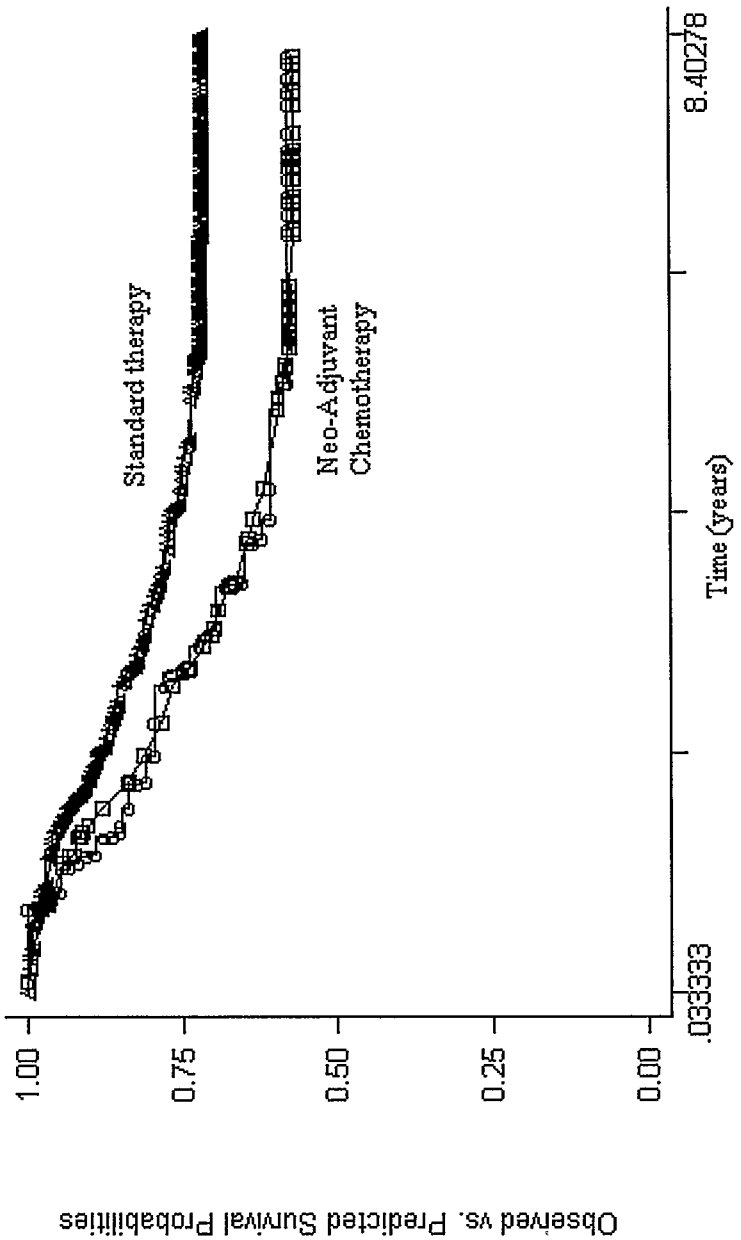


Figure 5 – Log – Log Plot by Disease Stage

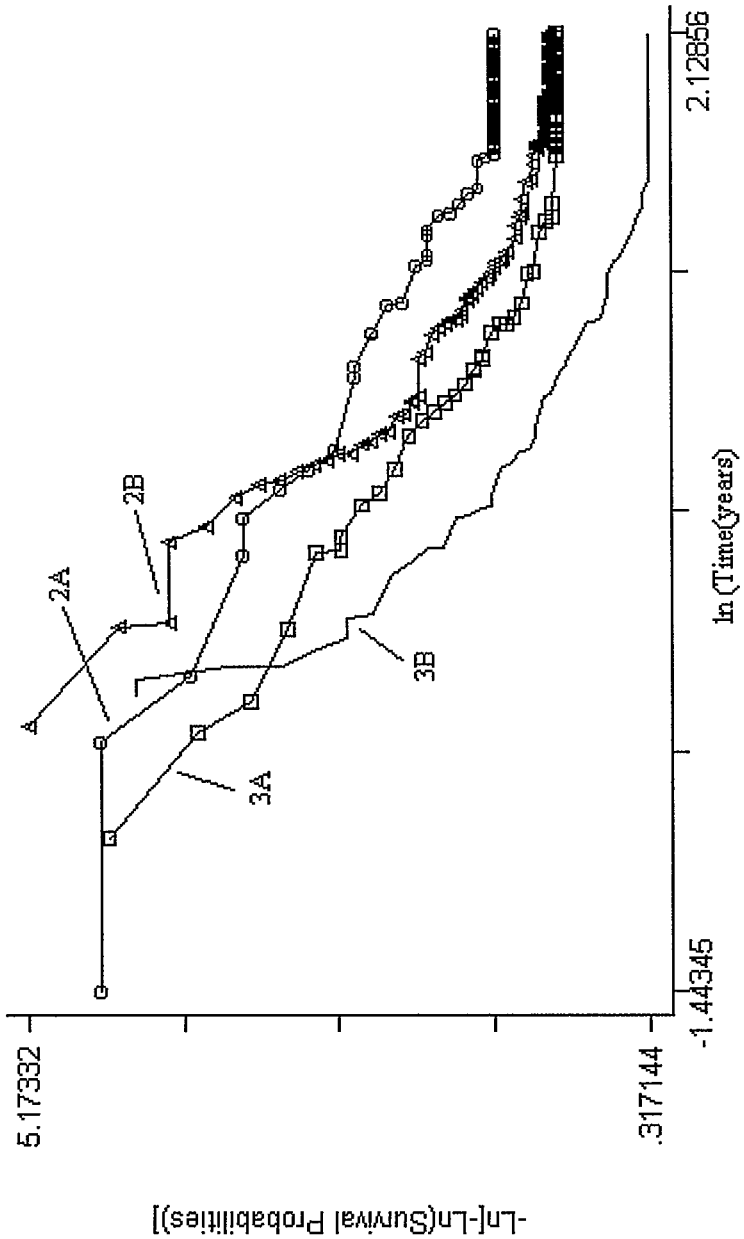


Figure 6 – Log – Log Plot by Histologic Grade

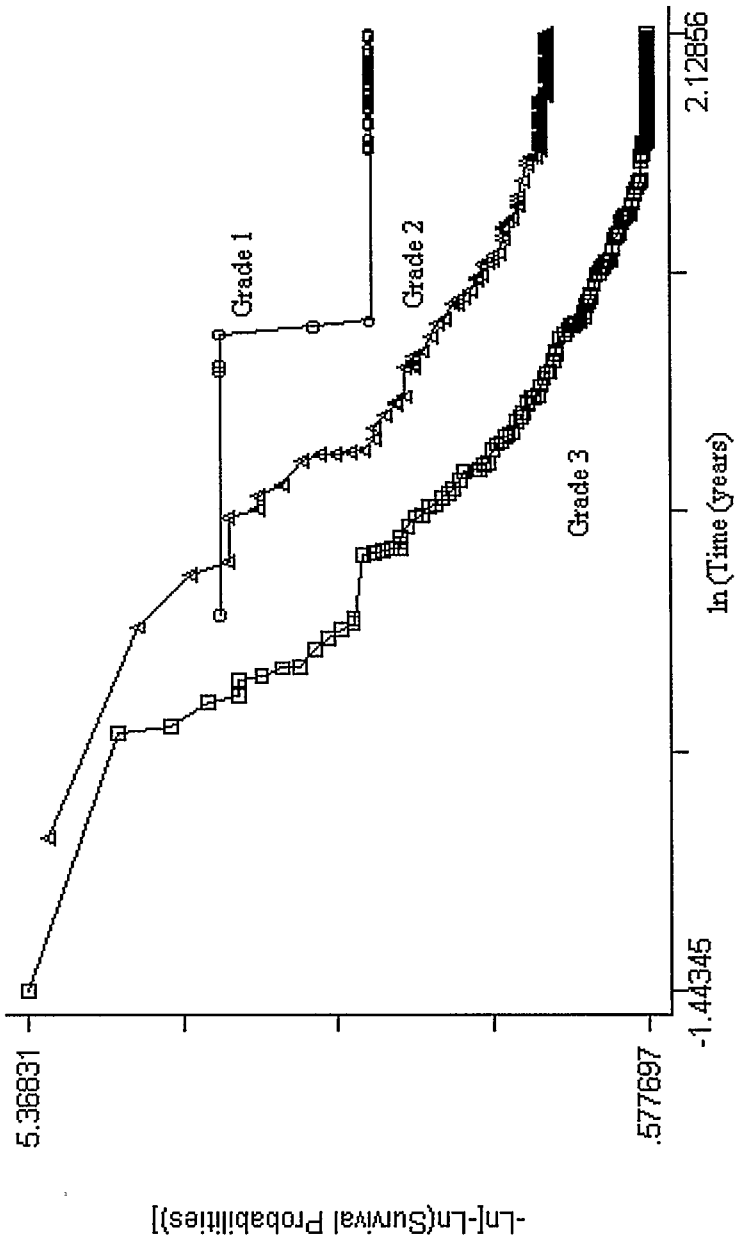


Figure 7 – Log – Log Plot by Hormone Therapy

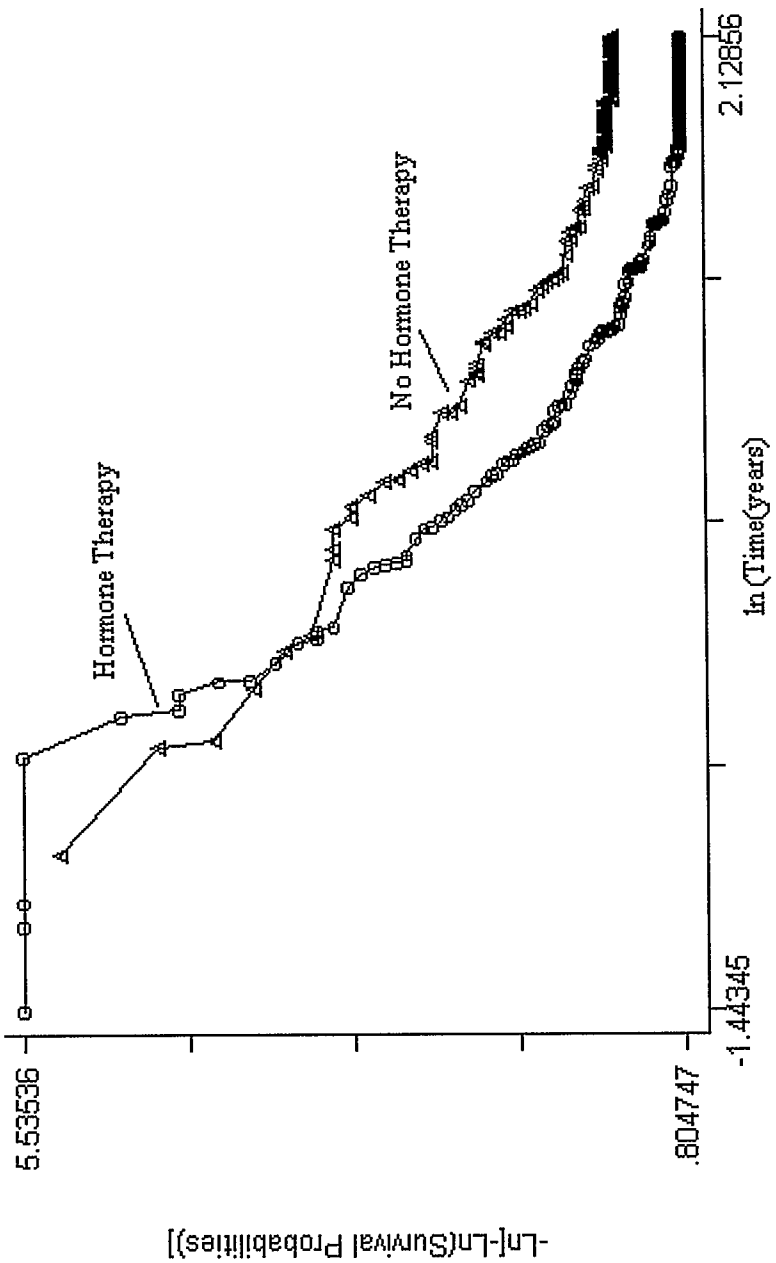


Figure 8 – Log – Log Plot by Treatment Type

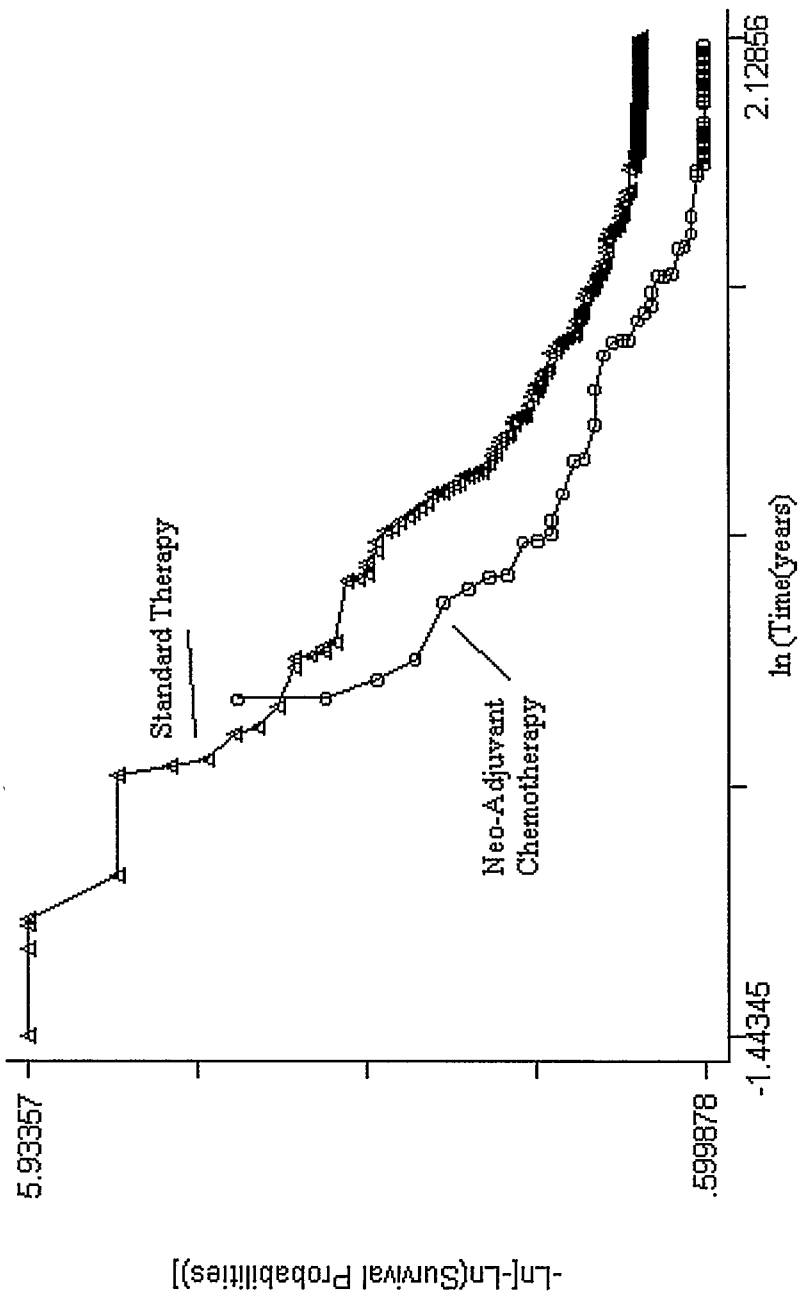


Figure 9 – Martingale Residuals Plotted by Disease Stage

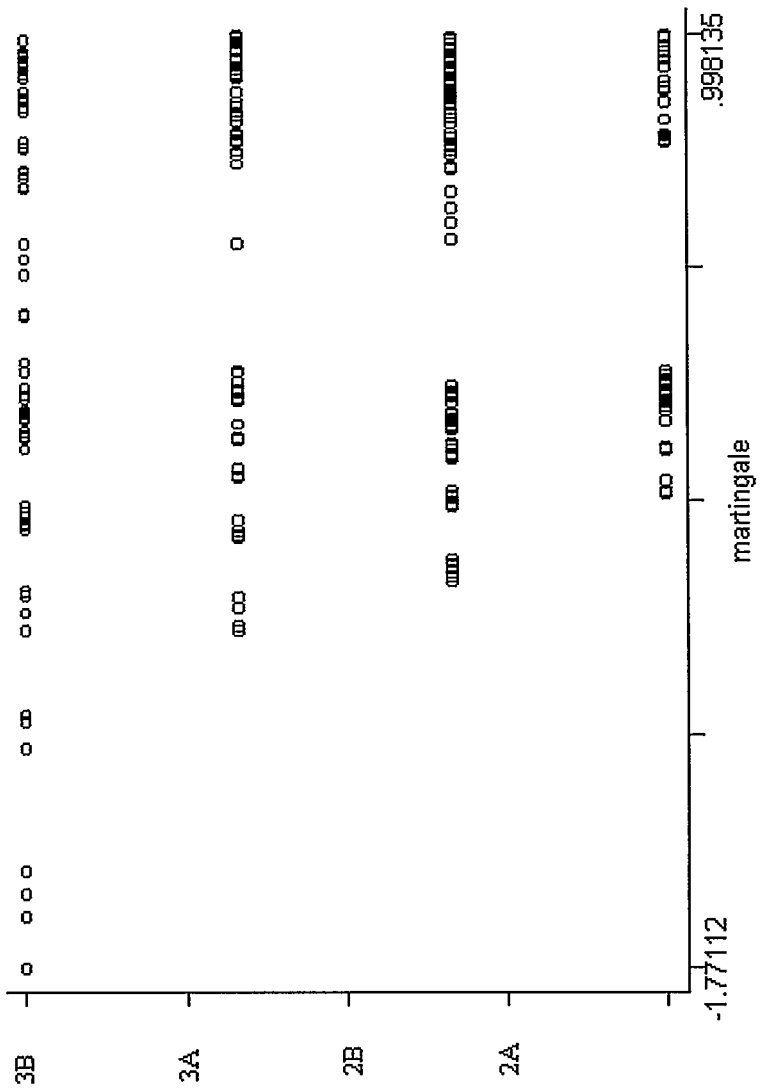


Figure 10 – Martingale Residuals Plotted by Histologic Grade

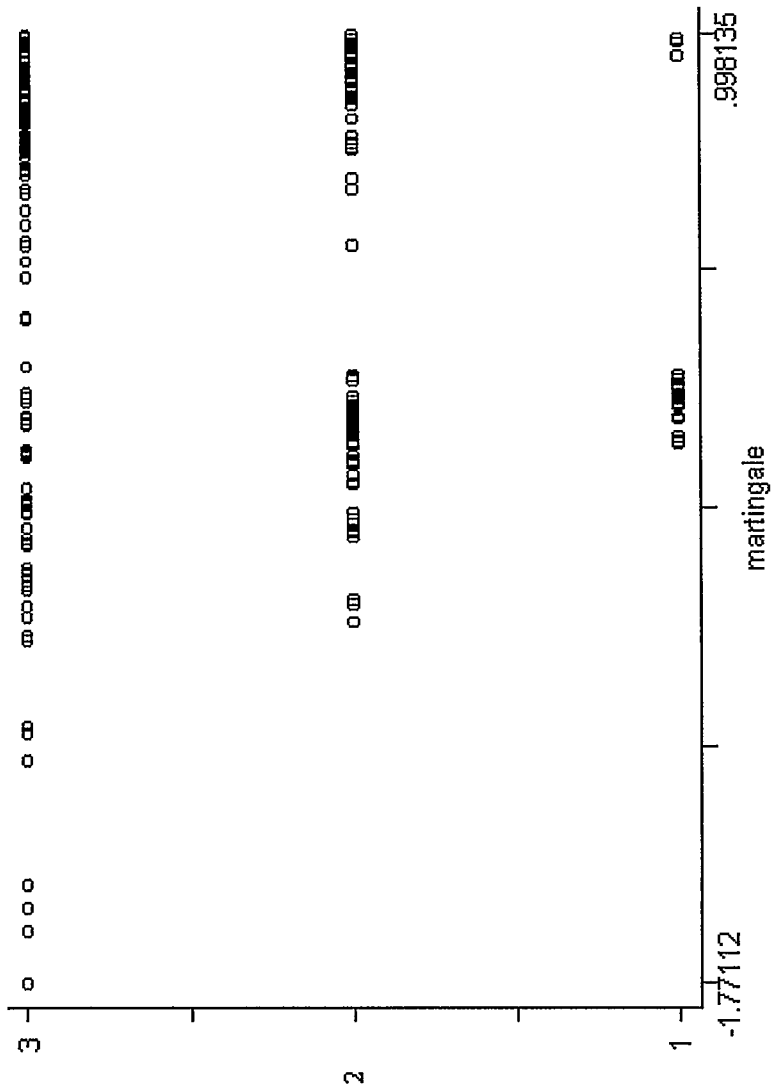


Figure 11 – Martingale Residuals Plotted by Treatment Type

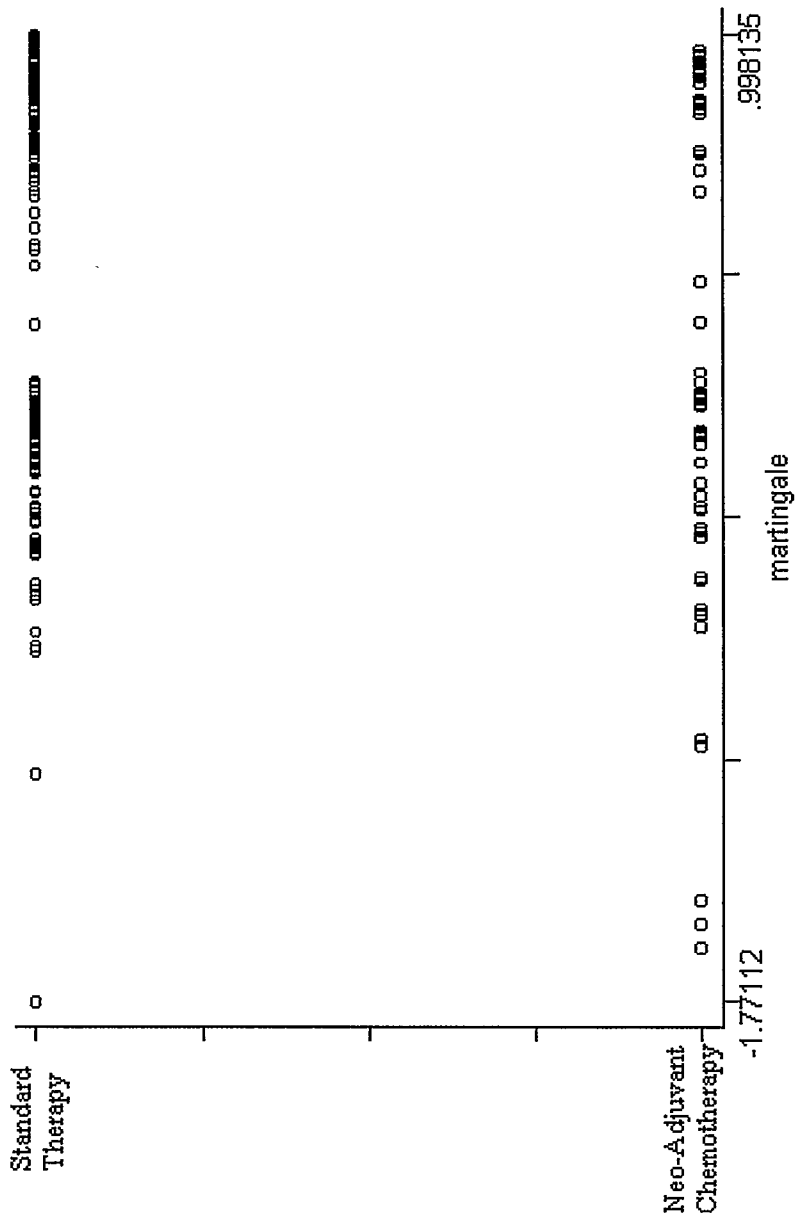
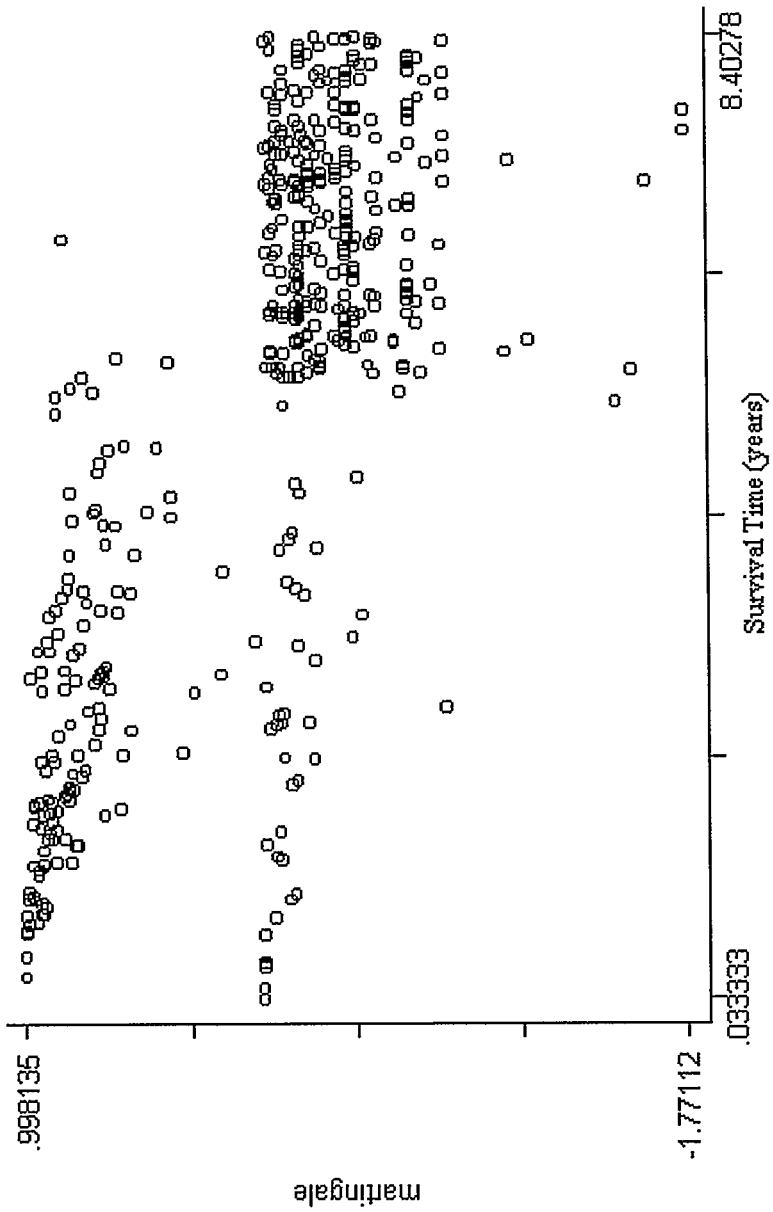


Figure 12 – Martingale Residuals Plotted by Survival Time (years)



Appendix B

Decision Analysis Literature Search References

[1-67]

1. Allen, M.W., et al., *A study on the cost effectiveness of sestamibi scintimammography for screening women with dense breasts for breast cancer.* Breast Cancer Res Treat, 1999. **55**(3): p. 243-58.
2. Allen, M.W., et al., *Decision analysis for the cost effectiveness of sestamibi scintimammography in minimizing unnecessary biopsies.* Q J Nucl Med, 2000. **44**(2): p. 168-85.
3. Armstrong, K., et al., *Cost-effectiveness of raloxifene and hormone replacement therapy in postmenopausal women: impact of breast cancer risk.* Obstet Gynecol, 2001. **98**(6): p. 996-1003.
4. Bates, M., et al., *A pharmacoeconomic evaluation of the use of dexrazoxane in preventing anthracycline-induced cardiotoxicity in patients with stage IIIB or IV metastatic breast cancer.* Clin Ther, 1997. **19**(1): p. 167-84.
5. Bordeleau, L., et al., *A comparison of four treatment strategies for ductal carcinoma in situ using decision analysis.* Cancer, 2001. **92**(1): p. 23-9.
6. Brown, R.E. and J. Hutton, *Cost-utility model comparing docetaxel and paclitaxel in advanced breast cancer patients.* Anticancer Drugs, 1998. **9**(10): p. 899-907.
7. Brown, R.E., J. Hutton, and A. Burrell, *Cost effectiveness of treatment options in advanced breast cancer in the UK.* Pharmacoeconomics, 2001. **19**(11): p. 1091-102.
8. Carter, K.J., et al., *Analysis of three decision-making methods: a breast cancer patient as a model.* Med Decis Making, 1999. **19**(1): p. 49-57.
9. Carter, K.J., et al., *Treatment of early-stage breast cancer in the elderly: a health-outcome- based approach.* Med Decis Making, 1998. **18**(2): p. 213-9.
10. Chen, Y.S., et al., *A review of the cost-effectiveness of Tc-99m sestamibi scintimammography in diagnosis of breast cancer in Taiwanese women with indeterminate mammographically dense breast.* Surg Oncol, 2002. **11**(3): p. 151-5.
11. Col, N.F., et al., *Survival impact of tamoxifen use for breast cancer risk reduction: projections from a patient-specific Markov model.* Med Decis Making, 2002. **22**(5): p. 386-93.
12. Collaco, L.M., et al., *Value of fine needle aspiration in the diagnosis of breast lesions.* Acta Cytol, 1999. **43**(4): p. 587-92.
13. Desch, C.E., et al., *Should the elderly receive chemotherapy for node-negative breast cancer? A cost-effectiveness analysis examining total and active life-expectancy outcomes.* J Clin Oncol, 1993. **11**(4): p. 777-82.
14. Dranitsaris, G. and T. Hsu, *Cost utility analysis of prophylactic pamidronate for the prevention of skeletal related events in patients with advanced breast cancer.* Support Care Cancer, 1999. **7**(4): p. 271-9.
15. Dranitsaris, G., et al., *Cost-utility analysis of second-line hormonal therapy in advanced breast cancer: a comparison of two aromatase inhibitors to megestrol acetate.* Anticancer Drugs, 2000. **11**(7): p. 591-601.

16. Extermann, M., L. Balducci, and G.H. Lyman, *What threshold for adjuvant therapy in older breast cancer patients?* J Clin Oncol, 2000. **18**(8): p. 1709-17.
17. Grann, V.R., et al., *Effect of prevention strategies on survival and quality-adjusted survival of women with BRCA1/2 mutations: an updated decision analysis.* J Clin Oncol, 2002. **20**(10): p. 2520-9.
18. Grann, V.R., et al., *Prevention with tamoxifen or other hormones versus prophylactic surgery in BRCA1/2-positive women: a decision analysis.* Cancer J Sci Am, 2000. **6**(1): p. 13-20.
19. Grann, V.R., et al., *Decision analysis of prophylactic mastectomy and oophorectomy in BRCA1- positive or BRCA2-positive patients.* J Clin Oncol, 1998. **16**(3): p. 979-85.
20. Grann, V.R., et al., *Benefits and costs of screening Ashkenazi Jewish women for BRCA1 and BRCA2.* J Clin Oncol, 1999. **17**(2): p. 494-500.
21. Hayman, J.A., et al., *Cost-effectiveness of adding an electron-beam boost to tangential radiation therapy in patients with negative margins after conservative surgery for early-stage breast cancer.* J Clin Oncol, 2000. **18**(2): p. 287-95.
22. Hayman, J.A., et al., *Cost-effectiveness of routine radiation therapy following conservative surgery for early-stage breast cancer.* J Clin Oncol, 1998. **16**(3): p. 1022-9.
23. Hershman, D., et al., *Outcomes of tamoxifen chemoprevention for breast cancer in very high- risk women: a cost-effectiveness analysis.* J Clin Oncol, 2002. **20**(1): p. 9-16.
24. Hillner, B.E., *Decision analysis: MIBI imaging of nonpalpable breast abnormalities.* J Nucl Med, 1997. **38**(11): p. 1772-8.
25. Hillner, B.E., H.D. Bear, and L.L. Fajardo, *Estimating the cost-effectiveness of stereotaxic biopsy for nonpalpable breast abnormalities: a decision analysis model.* Acad Radiol, 1996. **3**(4): p. 351-60.
26. Hillner, B.E., et al., *Trade-offs between survival and breast preservation for three initial treatments of ductal carcinoma-in-situ of the breast.* J Clin Oncol, 1996. **14**(1): p. 70-7.
27. Hillner, B.E. and T.J. Smith, *Efficacy and cost effectiveness of adjuvant chemotherapy in women with node-negative breast cancer. A decision-analysis model.* N Engl J Med, 1991. **324**(3): p. 160-8.
28. Hillner, B.E. and T.J. Smith, *Should women with node-negative breast cancer receive adjuvant chemotherapy?--Insights from a decision analysis model.* Breast Cancer Res Treat, 1992. **23**(1-2): p. 17-27.
29. Hillner, B.E. and T.J. Smith, *A model of chemotherapy in node-negative breast cancer.* J Natl Cancer Inst Monogr, 1992. **11**: p. 143-9.
30. Hillner, B.E. and T.J. Smith, *Cost effectiveness and other assessments of adjuvant therapies for early breast cancer.* Oncology (Huntingt), 1995. **9**(11 Suppl): p. 129-34.
31. Hillner, B.E., T.J. Smith, and C.E. Desch, *Efficacy and cost-effectiveness of autologous bone marrow transplantation in metastatic breast cancer. Estimates using decision analysis while awaiting clinical trial results.* Jama, 1992. **267**(15): p. 2055-61.

32. Hillner, B.E., T.J. Smith, and C.E. Desch, *Assessing the cost effectiveness of adjuvant therapies in early breast cancer using a decision analysis model.* Breast Cancer Res Treat, 1993. **25**(2): p. 97-105.
33. Hutton, J., et al., *A new decision model for cost-utility comparisons of chemotherapy in recurrent metastatic breast cancer.* Pharmacoeconomics, 1996. **9**(Suppl 2): p. 8-22.
34. Jackson, J.S., et al., *A decision analysis of the effect of avoiding axillary lymph node dissection in low risk women with invasive breast carcinoma.* Cancer, 2000. **88**(8): p. 1852-62.
35. Jacobs, H.J., et al., *Routine follow-up examinations in breast cancer patients have minimal impact on life expectancy: a simulation study.* Ann Oncol, 2001. **12**(8): p. 1107-13.
36. Johnston, K., *Modelling the future costs of breast screening.* Eur J Cancer, 2001. **37**(14): p. 1752-8.
37. Karnon, J. and J. Brown, *Tamoxifen plus chemotherapy versus tamoxifen alone as adjuvant therapies for node-positive postmenopausal women with early breast cancer: a stochastic economic evaluation.* Pharmacoeconomics, 2002. **20**(2): p. 119-37.
38. Kerlikowske, K., et al., *Continuing screening mammography in women aged 70 to 79 years: impact on life expectancy and cost-effectiveness.* Jama, 1999. **282**(22): p. 2156-63.
39. Launois, R., et al., *A cost-utility analysis of second-line chemotherapy in metastatic breast cancer. Docetaxel versus paclitaxel versus vinorelbine.* Pharmacoeconomics, 1996. **10**(5): p. 504-21.
40. Launois, R.J., J.M. Reboul-Marty, and J. Bonneterre, *[A medico-economic evaluation of second line chemotherapy in metastatic breast cancer: comparison between docetaxel, paclitaxel, and vinorelbine].* Bull Cancer, 1997. **84**(7): p. 709-21.
41. Layfield, L.J., et al., *The palpable breast nodule. A cost-effectiveness analysis of alternate diagnostic approaches.* Cancer, 1993. **72**(5): p. 1642-51.
42. Lee, J.H., et al., *Decision-analytic model and cost-effectiveness evaluation of postmastectomy radiation therapy in high-risk premenopausal breast cancer patients.* J Clin Oncol, 2002. **20**(11): p. 2713-25.
43. Leung, P.P., et al., *Cost-utility analysis of chemotherapy using paclitaxel, docetaxel, or vinorelbine for patients with anthracycline-resistant breast cancer.* J Clin Oncol, 1999. **17**(10): p. 3082-90.
44. Li, N., et al., *A cost--utility analysis comparing second-line chemotherapy schemes in patients with metastatic breast cancer.* Anticancer Drugs, 2001. **12**(6): p. 533-40.
45. Lindfors, K.K. and C.J. Rosenquist, *Needle core biopsy guided with mammography: a study of cost- effectiveness.* Radiology, 1994. **190**(1): p. 217-22.
46. Lindgren, P., et al., *Cost-effectiveness analysis of exemestane compared with megestrol in advanced breast cancer: a model for Europe and Australia.* Pharmacoeconomics, 2002. **20**(2): p. 101-8.
47. Mandelblatt, J.S., et al., *Breast cancer screening for elderly women with and without comorbid conditions. A decision analysis model.* Ann Intern Med, 1992. **116**(9): p. 722-30.

48. Messecar, D.C., *Mammography screening for older women with and without cognitive impairment.* J Gerontol Nurs, 2000. **26**(4): p. 14-24; quiz 52-3.
49. Noe, L.L., et al., *The cost effectiveness of tamoxifen in the prevention of breast cancer.* Am J Manag Care, 1999. **5**(6 Suppl): p. S389-406.
50. Nuijten, M., et al., *Cost effectiveness of letrozole in the treatment of advanced breast cancer in postmenopausal women in the UK.* Pharmacoeconomics, 1999. **16**(4): p. 379-97.
51. Orr, R.K., N.F. Col, and K.M. Kuntz, *A cost-effectiveness analysis of axillary node dissection in postmenopausal women with estrogen receptor-positive breast cancer and clinically negative axillary nodes.* Surgery, 1999. **126**(3): p. 568-76.
52. Parmigiani, G., et al., *Is axillary lymph node dissection indicated for early-stage breast cancer? A decision analysis.* J Clin Oncol, 1999. **17**(5): p. 1465-73.
53. Robinson, B.E. and L. Balducci, *Breast lump in an 85-year-old woman with dementia: a decision analysis.* J Am Geriatr Soc, 1995. **43**(3): p. 282-5.
54. Rosenquist, C.J. and K.K. Lindfors, *Screening mammography in women aged 40-49 years: analysis of cost- effectiveness.* Radiology, 1994. **191**(3): p. 647-50.
55. Rosenquist, C.J. and K.K. Lindfors, *Screening mammography beginning at age 40 years: a reappraisal of cost- effectiveness.* Cancer, 1998. **82**(11): p. 2235-40.
56. Salzmann, P., K. Kerlikowske, and K. Phillips, *Cost-effectiveness of extending screening mammography guidelines to include women 40 to 49 years of age.* Ann Intern Med, 1997. **127**(11): p. 955-65.
57. Schrag, D., et al., *Decision analysis--effects of prophylactic mastectomy and oophorectomy on life expectancy among women with BRCA1 or BRCA2 mutations.* N Engl J Med, 1997. **336**(20): p. 1465-71.
58. Schrag, D., et al., *Life expectancy gains from cancer prevention strategies for women with breast cancer and BRCA1 or BRCA2 mutations.* Jama, 2000. **283**(5): p. 617-24.
59. Smith, T.J. and B.E. Hillner, *The efficacy and cost-effectiveness of adjuvant therapy of early breast cancer in premenopausal women.* J Clin Oncol, 1993. **11**(4): p. 771-6.
60. Tengs, T.O., et al., *Testing for the BRCA1 and BRCA2 breast-ovarian cancer susceptibility genes: a decision analysis.* Med Decis Making, 1998. **18**(4): p. 365-75.
61. Unic, I., et al., *Prophylactic mastectomy or screening in women suspected to have the BRCA1/2 mutation: a prospective pilot study of women's treatment choices and medical and decision-analytic recommendations.* Med Decis Making, 2000. **20**(3): p. 251-62.
62. van Roosmalen, M.S., et al., *Decision analysis of prophylactic surgery or screening for BRCA1 mutation carriers: a more prominent role for oophorectomy.* J Clin Oncol, 2002. **20**(8): p. 2092-100.
63. Velanovich, V., *Immediate biopsy versus observation for abnormal findings on mammograms: an analysis of potential outcomes and costs.* Am J Surg, 1995. **170**(4): p. 327-32.
64. Velanovich, V., *Axillary lymph node dissection for breast cancer: a decision analysis of T1 lesions.* Ann Surg Oncol, 1998. **5**(2): p. 131-9.

65. Verhoef, L.C., et al., *Breast-conserving treatment or mastectomy in early breast cancer: a clinical decision analysis with special reference to the risk of local recurrence.* Eur J Cancer, 1991. **27**(9): p. 1132-7.
66. Warde, P. and A.S. Detsky, *Is steroid receptor data useful in patients with metastatic breast cancer?* Am J Med Sci, 1992. **304**(1): p. 9-13.
67. Wong, S.L., et al., *Optimal use of sentinel lymph node biopsy versus axillary lymph node dissection in patients with breast carcinoma: a decision analysis.* Cancer, 2002. **95**(3): p. 478-87.

Appendix C: Ethics Approval Form

UNIVERSITY OF CALGARY

FACULTY OF MEDICINE

Office of Medical Bioethics
Heritage Medical Research Building/Rm 93
Telephone: (403) 220-7990
Fax: (403) 283-8524

17 May 2002

Dr. L. Cook
Department of Community Health Sciences
HMRB
Calgary, Alberta

Dear Dr. Cook:

RE: Treatment Options In Locally Advanced Breast Cancer
Dr. Lea Austen (MSc Thesis)

Grant-ID: 16525

The above-noted thesis proposal has been submitted for Committee review and found to be ethically acceptable. Please note that this approval is subject to the following conditions:

(1) a copy of the informed consent form must have been given to each research subject, if required for this study;
(2) a Progress Report must be submitted by 2003-05-17, containing the following information:
    (i) the number of subjects recruited;
    (ii) a description of any protocol modification;
    (iii) any unusual and/or severe complications, adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
    (iv) a summary of any recent literature, finding, or other relevant information, especially information about risks associated with the research;
    (v) a copy of the current informed consent form;
    (vi) the expected date of termination of this project;
(3) a Final Report must be submitted at the termination of the project.

Please note that you have been named as a principal collaborator on this study because students are not permitted to serve as principal investigators. Please accept the Board's best wishes for success in your research.

Yours sincerely,

Christopher J. Doig, MD, MSc, FRCPC
Chair, Conjoint Health Research Ethics Board

cc: Adult Research Committee Dr. L. Sutherland (information) Dr. Lea Austen