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Effect of delay in initiating radiotherapy in patients with early-stage breast cancer: Results of a natural experiment

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Preface

Regulations for a Manuscript-based Thesis

Faculty of Graduate Studies and Research, McGill University

1. Candidates have the option of including, as part of the thesis, the text of one or more papers submitted or to be submitted for publication, or the clearly duplicated text (not the reprints) of one or more published papers. These texts must conform to the "Thesis Preparation Guidelines" with respect to font size, line spacing, and margins sizes and must be bound together as an integral part of the thesis.

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3. In addition to the manuscript per se, the thesis must conform to other requirements set out in the "Thesis Preparation Guidelines". The thesis must include the following: a table of contents; an abstract in English and in French; an introduction which clearly states the rationale and objectives of the research; a comprehensive literature review; a final conclusion and summary; and, rather than an individual reference list after each chapter or paper, one comprehensive bibliography or reference list at the end of the thesis, after the final conclusion and summary.

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Abstract

Background: For stage I and II breast cancer, the standard treatment is partial mastectomy followed by radiation treatment. The risk of local recurrence ranges from 6 to 9%. A controversy exists as to whether there is an increased risk of local recurrence as a result of excessive delay between surgery and radiation treatment. A natural experiment associated with a prolonged waiting time in our institution provided an opportunity to evaluate the impact of waiting times for radiation treatment of breast cancer on the risk of local recurrence.

Methods: Between January 1988 and December 1989, 486 patients with stage I or II breast cancer from McGill hospitals were treated with radiotherapy. Their charts were reviewed, and information with regard to prognostic factors, such as age, tumor size, histological grade, number of positive lymph nodes, and margins of resection, was abstracted. The interval between the date of surgery and the date of initial radiation treatment, and events, such as local recurrence, metastases and death, were noted.

Results: At five years, the local recurrence rate was 8%, the metastatic rate 13%, and the disease-free survival rate 89%. In the univariate analysis, the risk of local recurrence was associated with younger age, higher histological grade, and time to radiation treatment. In the multivariate Cox proportional hazard models, higher histological grade and time to radiation treatment were significant. Using recursive partitioning, the risk of local recurrence was almost five times higher for patients who waited in excess of 79 days for radiation treatment.

Conclusion: Delay in radiation treatment is associated with an increased risk of local recurrence of breast cancer.

Keywords: Radiotherapy, breast cancer, delay, recurrence, outcome, health services research.

Résumé

Introduction: Pour les cancers du sein stades I et II, le traitement stantard est la mastectomie partielle suivie d'irradiation. Le risque de récidive locale est de six à neuf pour cent. Une contreverse existe quant à une augmentation du risque de récidive locale lié a un délai excessif entre la chirurgie et le début des traitements par radiothérapie. Une expérience naturelle associée aux délais observés dans notre institution nous a donné l'opportunité d'évaluer l'impact du temps d'attente pour la radiothérapie sur le risque de récidive locale dans le cancer du sein.

Méthodes: De janvier 1988 à décembre 1989, 486 patientes avec un cancer du sein stade I et II furent traitées par radiothérapie à l'université McGill. Leurs dossiers cliniques furent revus, et les informations concernant les facteurs prognostiques, tels que l'âge de la patiente, la taille de la tumeur, le grade histologique, le nombre de ganglions envahis, et les marges de resection après chirurgie furent collectés. L'intervalle de temps entre la date de chirurgie et la date de début de radiothérapie, et les événements tels que récidive locale, métastase, et décès furent recueillis.

Résultats: Avec 5 ans de suivi, le taux de récidive locale était de 8%, le taux de métastases 13%, et la survie 89%. Dans l'analyse univariée, le risque de récidive locale était associé avec le jeune âge, un grade histologique plus élevé, et un délai pour les traitements par radiothérapie. Dans l'analyse multivariée, utilisant le modèle de Cox, le grade histologique plus élevé et le délai pour la radiothérapie restaient des facteurs statistiquement significatifs. En utilisant un modèle de partition récursive, le risque de récidive locale fut trouvé à presque 5 fois plus élevé pour les patientes qui attendaient plus de 79 jours pour leur radiothérapie.

Conclusion: Le délai pour débuter la radiothérapie est associé avec un risque plus élevé de récidive locale dans le cancer du sein.

1. Introduction

Breast cancer remains a major cause of morbidity and mortality in Canada. Conservative management of early-stage breast cancer with wide local excision followed by radiation treatment of the remaining breast tissue is widely accepted as standard practice based on multiple prospective and retrospective studies (1-4). Using this treatment approach, five-year local recurrence rates have been found to be in the range of 6 to 9% (2,5-8). Several factors have been shown to influence the risk of developing a local recurrence, including the extent of surgery and margin assessment, the histological grade, the presence of an extensive intraductal component, and the patient's age (9). Given the substantial proportion of patients who develop a local recurrence, it would be important to determine whether there are any additional factors that affect the risk of local recurrence which could be altered.

A recently published Canadian consensus document sets out clinical practice guidelines for the care and treatment of breast cancer. The Steering Committee recommended that all women who undergo breast-conserving surgery should be advised to have postoperative radiation treatment to decrease the risk of local recurrence. The treatment should be started as soon as possible but no later than 12 weeks after surgery (9). However, they recognized that the optimal interval between surgery and the start of irradiation has not been determined. In theory, for patients not receiving chemotherapy, radiation treatment could start as soon as the surgical scar has healed properly, generally two weeks after surgery. In fact, average waiting times for radiation treatment have been lengthening over the past decade in Canada (10). Through a survey of

radiotherapy facilities in Canada and the United States, MacKillop found that the average waiting time from referral to a radiation oncologist to the commencement of adjuvant radiotherapy for breast cancer was 43 days in Canada compared to only 10 days in the US (11). This study estimated waiting times only for those patients who had already accessed the health-care system and thus probably did not take into account financial barriers to access in the U.S. However, the markedly longer waiting times in Canadian centres were felt to be unacceptable by most of the American and Canadian radiation oncologists surveyed in this study.

There is concern that difficult access to radiation oncology departments may be resulting in adverse effects on patient outcomes, such as increased local recurrence rates and lower survival rates. Recently, survival rates for breast cancer have been reported to be different for American and Canadian patients, with women in the United States enjoying a survival advantage, most likely related to the promotion of earlier and therefore more efficacious treatment (12).

2. Objectives

2.1 Primary Objective

To determine whether the length of time between the excision of the primary tumour and the commencement of adjuvant radiotherapy influences the risk of local recurrence in women with stage I or stage II breast cancer.

2.2 Secondary Objectives

To ascertain which patient-related and health care system-related factors, in addition to time to radiation treatment, influence the risk of local recurrence of cancer and which factors influence the waiting time between surgery and the start of irradiation.

3. Background and Rationale

3.1 Clinical guidelines for the treatment of early breast cancer

Women with early breast cancer, or stage I or stage II disease, have the following features based on the American Joint Committee on Cancer (AJCC) staging recommendations (13). Stage I breast cancer is defined as a primary tumour of up to 2 cm in greatest dimension, without ipsilateral axillary node involvement, and stage II is defined as a primary tumour of up to 5 cm with or without ipsilateral axillary node involvement, but without fixation of the nodes to one another or to other structures.

For patients with stage I or II breast cancer, breast-conserving surgery (BCS) and axillary-lymph-node dissection followed by radiotherapy are recommended by the Canadian Steering Committee in the Clinical Practice Guidelines for the Care and Treatment of Breast Cancer (9). BCS consists in removing the tumour along with a cuff of normal tissue while preserving the cosmetic appearance of the breast, and is also referred to as *lumpectomy* or *wide local excision*. Lymph-node dissection is the removal of the axillary lymph nodes for accurate staging and to reduce the risk of recurrence in the axilla. Pathology systematically reports the histology of the

tumor (ductal or lobular), its size, its histological grade (well, moderately or poorly differentiated), the status of the margins, the eventual presence of ductal carcinoma in situ, the hormonal receptor status and the number of lymph nodes removed and involved. Six prospective, randomized, controlled trials have shown that in patients with operable breast cancer, the outcome after BCS with radiotherapy was equivalent to that of mastectomy with respect to local and distant recurrences and overall survival (9). The trial with the highest statistical power was National Surgical Adjuvant Breast Project (NSABP) multicenter protocol B-06, which compared BCS with and without radiotherapy to mastectomy in 1843 women with stage I or II tumours in whom BCS was cosmetically feasible (2). Tumours were excised with clear margins, that is no malignant cells at the cut surface on microscopic examination, but no minimum width was required. After an average of 12 years of follow-up, disease-free survival and overall survival were still identical in patients treated by BCS with or without radiotherapy and in those treated by mastectomy, although local recurrence was much more frequent (35% vs 10%) when radiotherapy was omitted after BCS. Thus, lumpectomy followed by radiation treatment provides very adequate long-term local control, and in the absence of special reasons for selecting complete mastectomy, the choice between BCS and complete mastectomy can be made according to the patient's circumstances and personal preferences.

For patients receiving radiation therapy, the recommended treatment is whole-breast irradiation, with opposed tangential fields using a cobalt 60 unit or a 6-MV linear accelerator. The commonest fractionation schedule in Canada is a total dose of 50 Gy given in fraction sizes of 2 Gy per day, 5 days per week, or in 25 fractions (9). The optimal fractionation schedule for breast

irradiation has not been established. However, indirect comparisons between studies using different fractionation schedules suggest that local recurrence, cosmetic outcome and survival are roughly comparable. Controversies exist regarding the advantage of boost irradiation to the primary site when the margins are clear. At least one randomized study has shown an advantage in terms of local control with boost irradiation (14). Other randomized trials evaluating the role of boost irradiation are in progress. However, for patients with a positive resection margin, a boost of 10 Gy in 5 fractions is usually given. In cases of apical axillary lymph-node involvement or extracapsular growth, the axilla and supraclavicular regions are routinely irradiated at a dose of 50 Gy in 25 fractions (15).

The decision to administer adjuvant systemic therapy is based on the patient's risk for distant recurrence, categorized as low, intermediate or high on the basis of the size of the tumour, its histological grade, the number of lymph nodes involved, the patient's age, her menopausal status, and her estrogen receptor status. Adjuvant systemic therapies, either chemotherapy or tamoxifen, are associated with a reduced risk of distant recurrence and mortality, but with a limited effect on local recurrence. Chemotherapy is recommended for all women at high risk for recurrence and may be considered for women at intermediate risk (9,16). The two standard chemotherapy regimens are of 6 cycles CMF (C: cyclophosphamide, M: methotrexate, F: fluorouracil) and 4 cycles of AC (A: adriamycin, C: cyclophosphamide). Radiation treatment is usually given concurrently with CMF or after completion of the AC regimen. Adjuvant endocrine treatment with tamoxifen is recommended for all women with estrogen receptor-positive tumours and is administered daily for 5 years (17). Whenever possible, patients are invited to participate in

clinical trials and therefore, guidelines for the timing of the irradiation should be observed.

Once the primary treatment is complete, patients are kept under surveillance for some years. In our institution, patients were followed at short intervals for 5 years, after which routine visits were carried out annually. Regular mammographic examinations were performed at 12 months interval. Laboratory tests, radiographic examination and scanning were only done when new, persistent symptoms were reported by the patient.

3.2 Existing literature on the risk of local recurrence.

The extent of surgery and the likelihood of margin involvement directly impact on the risk of local recurrence in the conserved breast. The adequacy of surgery is assessed by pathologic margin status. However, the process of reading pathology slides after applying India ink to the margins is a sampling exercise. Grossly involved margins are clearly associated with an increased risk of local recurrence (9). However, when margins are only microscopically involved, the risk of recurrence is less clear (18,19). The Institut Curie reported on a series of 394 women who received high-dose irradiation after a needle biopsy and found that 59% required secondary surgery for recurrent or persistent disease (20). The Joint Center for Radiation Therapy compared two cohorts of patients, one treated from 1968 to 1982, the other from 1983 to 1985 (21). The authors reported a trend towards improved local control in the more recent cohort, which they attributed to improved patient selection, as a result of evaluating specimen margins and re-excision in case of an extensive intraductal component or uncertain initial margins. However, Solin reported no increase in recurrence rates in the presence of microscopically positive margins

(22). Other microscopic features, such as poor histological grade or an extensive intraductal component were also associated with a higher likelihood of local recurrence (23,24). Tumour size has been correlated with a higher risk of local recurrence in some but not all studies (25).

The effect of young age on the prognosis of breast cancer is the subject of controversy. A review of the data on local control after breast-conserving therapy showed a trend towards an increased failure rate in the youngest patient subsets. Kurtz et al reported a 20% crude failure rate in patients younger than 40 compared to 9% for older patients(26). The younger patients were also more likely to have an extensive intraductal component and high histological grade tumours. However, patient age lost prognostic significance when all other risks factors were included in a multivariate analysis. At the Joint Center, young age, defined as less than 35 years, was associated with an increased risk of local failure, even after correction for the other risk factors (27).

3.3 Existing Literature on Waiting Times for Radiotherapy

3.3.1 Biological rationale

There is biological evidence supporting the view that delaying adjuvant radiotherapy has a detrimental effect on treatment outcome (28-32). Radiobiological studies suggest that the massive cell depletion that occurs with surgical excision of the primary tumour is a powerful stimulus for the growth of residual tumour cells, due to the release of growth factors secondary to tissue injury or via other mechanisms. Thus, within a short period of time following primary surgery, one might expect accelerated repopulation by any remaining tumour cells. Clinical data have been reported for head and neck cancers, and for cervical cancers which confirm that delay has an

effect on local control of the tumour (33,34). MacKillop et al has developed a mathematical model to estimate the effects of delay in radiotherapy for squamous cell carcinoma of the tonsillar region (35). Utilizing this model, it was estimated that the local control rate would decrease by approximately 10% after a delay of 30 days. Thus, one would anticipate that a prolonged delay between surgery and postoperative radiotherapy for patients with early-stage breast cancer may allow repopulation to occur to the extent that local control of the tumour is compromised.

3.3.2 Controversial literature on breast cancer

In the literature, a controversy has emerged regarding the possibility of an increased risk of local recurrence of breast cancer as a result of a delay between surgery and the initiation of radiation. For breast cancer patients with no indication of chemotherapy, Clarke et al analyzed local relapses in 436 women with early-stage breast cancer treated with surgical excision and radiotherapy, 45 Gy followed by a 15-Gy boost to the tumour bed, at a single institution from 1970 to 1981 (36). Using univariate analysis, he found that a delay greater than seven weeks, or 49 days, correlated with a higher relapse rate at 5 years (RR=3). In the multivariate analysis, when the three significant factors revealed by the univariate analysis were introduced in the model, the delay in initiating radiotherapy lost its significance. Whelan et al reviewed 400 patients irradiated with 40 Gy in 16 fractions followed by a boost of 12.5 Gy in 5 fractions to the primary site (37,38). Of them, 215 started radiotherapy within 8 weeks of surgery and 185 started it after 8 weeks of surgery. He reported at 8.4 years of follow-up a trend towards an increased risk of local recurrence with a delay greater than 8 weeks (56 days) in the univariate analysis (RR=1.7) and in the multivariate analysis (RR=1.6). In these two studies, no information on standard error (SE)

was given. It could be surmised that the confidence interval (CI) included zero, but the upper limit of the CI would be interesting from a clinical standpoint. Therefore, the results concerning delay in initiating radiotherapy in these studies are inconclusive. Slotman et al studied 508 patients with stage I or stage II breast cancer, with a median follow-up of 68 months (39). Overall, 3.3% of the patients experienced a local recurrence after a median interval of 36 months, a somewhat lower rate than that found in most studies, which suggests possible patient selection bias. However, there were no breast recurrences in the 42 patients who started radiotherapy within 25 days. The breast recurrence rate was 2% (5/256) in the patients with an interval of 25-50 days, 5.4% (10/184) in the patients with an interval of 50-75 days and 6.3% (2/32) in the patients with an interval longer than 75 days. The recurrence rate was 1.7% for the patients who received radiotherapy within 50 days of surgery and 5.6% where the time interval was longer. In the Cox proportional hazards analysis, the confidence interval limits for the interval between surgery and radiotherapy in days were 0.005 and 0.05. Therefore, the delay in radiation treatment could have a small effect. Tumour size and resection margin involvement were also found to significantly influence the risk of local recurrence.

In contrast, Nixon et al found that a delay of up to 8 weeks, or 56 days, was not associated with any increase in the risk of recurrence in a retrospective analysis of 653 patients with breast cancer receiving 45 Gy to the whole breast followed by a boost of 15 Gy (40). Patients treated 5-8 weeks after surgery did not differ significantly in rate of recurrence from patients treated 0-4 weeks after surgery (RR=0.89, no SE). Only 54 patients waited longer than 8 weeks. Consequently, the recurrence rates for these patients could not be meaningfully compared to those

for the 599 patients who waited for less than 8 weeks. Fourquet et al examined the records of 1839 patients with stage I or stage II breast cancer treated at a single institution over a period of eight years, with 50 Gy followed by a boost of 15 Gy (41). The local recurrence rates were 12% for the patients who waited less than 35 days after their surgery (n=1200), 9% for those who waited for 35-56 days (n=578), and 18% for those who waited for more than 56 days (n=61). The differences between the shorter and longer interval groups were not statistically significant (RR=1.5, no SE). However, the high risk of local recurrence in the first group suggests some selection bias, and the small number of patients with the longest waiting times makes it difficult to compare the recurrence rate in this group with those in the other two groups. Vujovic et al reviewed 568 node-negative stage I and II breast cancer patients with 63.5 months of follow-up (42). She suggested that a delay in initiating breast irradiation of up to 16 weeks, or 112 days, did not increase the risk of recurrence. In the Cox proportional hazards model, the 95% confidence interval limits for the different surgery-radiotherapy intervals were 0.99 and 1.014. Therefore, the delay in treatment may have had a small effect. However, only 41 patients (7%) had a delay longer than 16 weeks, and 54% of her patients received a boost to the tumour bed after conventional irradiation, a technique that Romestaing et al have shown to reduce the risk of local recurrence (14).

For patients receiving chemotherapy, radiotherapy is often delayed, the rationale being that metastatic disease poses a greater threat to the patient and that chemotherapy has at least some effect on any residual local disease. This strategy may not be optimal, however, since the risk of local recurrence may be greater when radiotherapy is delayed. In a review of 105 patients

treated with adjuvant chemotherapy followed by radiotherapy, with 45 Gy delivered to the breast and a 15-Gy boost, Buchholtz et al found, in a multivariate comparison, a significantly higher local recurrence rate ($p=0.011$), a lower disease-free survival rate ($p=0.009$) and a decreased overall survival rate ($p=0.05$) at 8 years in patients with breast cancer whose radiotherapy was delayed for more than six months, or 180 days, after diagnosis (43). Recht et al reviewed 295 patients with node-positive stage II breast cancer treated with different sequences of radiotherapy and chemotherapy (44). The actuarial 5-year local recurrence rate was 5% for the 252 patients who received radiotherapy within 16 weeks, or 112 days, of surgery compared to 35% for the 34 patients treated more than 16 weeks after surgery ($p=0.06$). Thereafter, they confirmed among 244 women with stage I or stage II breast cancer prospectively randomized to receive either the sequence chemotherapy-irradiation or the sequence irradiation-chemotherapy that the 5-year actuarial local recurrence rate was higher with a surgery-radiotherapy interval of 126 days compared to a delay of 52 days (13% vs 5%) (45). However, at 5 years, the distant recurrence rate was higher in the radiotherapy-first arm (32% vs 20%), and the overall survival rate was not statistically significant (73% vs 81%, $p=0.11$). Important prognostic factors appeared to be well distributed between the two groups, and median follow-up was 58 months. Hartsell et al reported only on 84 patients with node-positive breast cancer treated with breast-conserving therapy and chemotherapy with a median follow-up of 68 months (46). The relapse rate was 2% in the group irradiated before 120 days and 14% in the group receiving irradiation 120 days after surgery. All of the local recurrences were detected within 30 months of the initial diagnosis. However, in the multiple regression analysis, margin of resection was the only predictor of local recurrence. Surgery-radiotherapy interval was the next factor identified in the regression analysis but did not

reach statistical significance (p=0.09). In contrast, Heimann et al did not find a significant difference in local failure rates between patients whose radiotherapy was or not delayed (7% vs 5%, p=NS) in a study involving 166 patients representing a heterogeneous population and patients receiving chemotherapy before, during or after radiation (47).

In this literature review, the minimum follow-up was 60 months and the local failures were usually observed within 30 months after the initial diagnosis. Only one prospective study has been performed to answer the question of the impact of delay; it compared the sequence radiotherapy-chemotherapy with the sequence chemotherapy-radiotherapy (45). All the other trials have been retrospective, the design that lends itself best to the study of the impact of delay on outcome from an ethical standpoint. Technically, the radiation fractionation schedules ranged from 40 Gy in 16 fractions to 50 Gy in 25 fractions, which were or not followed by a boost of 10 to 16 Gy, reflecting variations in clinical practice. In summary, for time to radiation treatment of up to 56 days, only one author out of four was able to demonstrate in a univariate analysis an increased risk of local recurrence, but for time to radiation treatment between 75 and 180 days, five authors out of six reported an increased risk of local recurrence (Table 1).

3. 4 Existing literature on predictors of waiting time for radiotherapy.

If delays in commencing radiotherapy do lead to poorer patient outcomes, especially in terms of increased local recurrence rates, then it would be important to determine which factors are associated with increased waiting times. In general, delays in patient care may occur prior to the initial evaluation by a health care provider, in diagnosing the condition or in commencing the

appropriate treatment. Waiting times for adjuvant radiotherapy are related to delays in health care delivery, since patients have already accessed the health care system, had their cancers diagnosed and had a segmental mastectomy prior to waiting for radiotherapy. A number of factors related to the patient herself might also predispose her to longer waiting times. In one study, older cancer patients were found to be less likely to receive definitive treatment because of impaired access to transportation, poor social support, impaired cognitive status and reduced physical activity (48). Another study showed that American breast cancer patients who did not have private health insurance received less vigorous treatment and had more frequent adverse outcomes than patients with private insurance, findings that probably concern patients with lower incomes (49,50). As for health care system-related factors, Craighead and Ewing identified several associated with longer waiting times in radiation therapy facilities, including a delay in referral to a radiotherapy centre, increased investigation time, especially in more recent years, and shortages of radiation technologists and critical equipment, as well as scheduling inefficiencies and the restriction of equipment use to certain hours of the day (51). The findings of a survey concerning technical and staffing-level profiles in Canadian radiotherapy and involving all Canadian centres providing radiotherapy services in 1997 were recently reported (52). The conclusions were that, with respect to equipment, all provinces approach the average equipment workload calculated for Canada and provide all patients with access to modern cancer therapy technology. In Quebec, an infusion of capital in the early 1990's seemed to have settled the equipment workload issue. However, as regards staff workload, two "standards" were described, one for Quebec and one for the rest of Canada, with the staff workload for Quebec exceeding those for the rest of Canada by a considerable margin for all four professional groups in radiotherapy, i.e. radiation oncologists,

radiotherapists, clinical physicists and radiation dosimetrists. This shortage of staff results in increased waiting times for accessing radiation oncology facilities, with time taken by a consulting radiation oncologist before making an assessment, time before planning the treatment, and time for accessing the treatment units. In Quebec, equipment and personnel are under direct government control and are affected by the overall size of the radiation oncology departments' operating budgets. The level of resources available to treatment centers could therefore directly affect waiting times for radiation treatment after BCS.

3. 5 Previous Related Research

A previous retrospective pilot study conducted at McGill University hospitals involved women with stage I or II breast cancer treated with adjuvant radiotherapy (53, 54). This initial study involved 739 patients treated between January 1992 and December 1993 at the Montreal General Hospital (MGH), the Jewish General Hospital (JGH), and the Royal Victoria Hospital (RVH). It was performed to determine how long women were waiting before commencing adjuvant radiotherapy and to delineate those factors important in predicting delay. From the radiation oncology chart, the waiting time indicator for radiation treatment was tracked by recording the date of diagnosis recorded at the time of the definitive surgical procedure, the date of the first consultation with the radiation oncologist, and the treatment date, which was the date of the first radiation treatment. With these three dates, we measured the time to radiation treatment from the date of surgery to the date of the first radiation treatment, the time to consultation from the date of surgery to the date of the first consultation in the radiation oncology department, and the time to treatment unit from the date of the first evaluation to the date of the

first radiation treatment.

Using a time to radiation treatment greater than seven weeks for women not receiving chemotherapy (NC group = 478) and a time to radiation treatment greater than 24 weeks for those women receiving chemotherapy (C group = 261) as definitions for excessive delay, 54% of the patients were found to be excessively delayed in starting radiotherapy (72% of the patients in the NC group and 22% in the C group) (36,43). The waiting times varied immensely, ranging from one to 34 weeks in the NC group, and from two to 50 weeks in the C group. One sixth to one half of this waiting time was found to be related to time to treatment unit (33/68 days in the NC group, 36/222 days in the C group), the remaining time being time to consultation.

The referring institution was found to be an important potential predictive factor for delay. A teaching institution was defined as a facility affiliated with a medical school and/or which has resident physicians providing patient care. In the NC group, women referred from teaching hospitals were found to be more likely to experience a delay in receiving radiotherapy than women referred from nonteaching hospitals. In the C group, women referred from a nonteaching hospital had increased waiting times compared to those referred from a teaching hospital. Thus, the influence of being referred from a teaching or nonteaching hospital is not clear. In the C group, women with stage II disease and/or not on a study protocol were also delayed. Whether or not income has an impact on waiting time was also investigated, but no impact was found. To determine the patients' incomes, we used the residential postal codes published annually by Statistics Canada (55). This variable is commonly accepted as a surrogate for a patient's income

or wealth in the literature, though it is clearly only an approximate indicator, given the degree of income variability within a given postal code area (56,57).

From this previous research, we determined that more than half of our patients were delayed in 1992-1993 due to a combination of time to consultation and time to treatment unit, and confirmed that lower-income patients did not wait longer than higher-income patients, possibly as a result of Canada's medicare system. This study identified some of the factors responsible for waiting time for radiation treatment, but no data on local recurrence rates or how they are related to waiting times for radiotherapy were collected. Delays in radiation treatment still being a reality at our institution, our goal was to determine if waiting time had an impact on local control. To obtain information on local recurrence rates, a minimum follow-up of five years was necessary. Therefore, we decided to collect information on patients treated in 1988-1989.

4. Methods

4.1 Study Design

This is a retrospective cohort study involving women with early-stage breast cancer treated with postoperative adjuvant radiotherapy between January 1, 1988 and December 31, 1989 at the three institutions affiliated with McGill University that provide all radiation therapy services: the Montreal General Hospital (MGH), the Jewish General Hospital (JGH) and the Royal Victoria Hospital (RVH). Radiation oncologists at each of these institutions were contacted, and they indicated their willingness to participate in this study.

4. 2 Study Sample

4.2.1 Inclusion criteria

From the computerized system that registers all patients receiving radiation treatment at our institution we obtained the list of all patients with stage I or II breast cancer treated between January 1, 1988 and December 31, 1989 at McGill University. The final study sample consisted of 486 women referred to the Department of Radiation Oncology after breast-conserving surgery and axillary lymph node dissection. Women with invasive breast cancer of any histology, ductal or lobular, were included.

4.2.2 Exclusion criteria

Women referred for radiotherapy to the chest wall following modified radical mastectomy were excluded from the study sample. Women treated with radiotherapy for ductal carcinoma in situ (DCIS) were excluded unless histological evidence of invasive carcinoma was also present. Women whose primary tumour extended directly to the skin or chest wall, as in the case of inflammatory breast cancer (T4 disease), whose disease involved ipsilateral internal mammary lymph nodes (N3 disease), or whose malignancy had spread to distant sites (M1 disease) were not included in the study population. No patients were excluded on the basis of age, concomitant medical problems or any other patient-related factors.

4. 3 Outcome Measures

4.3.1 Primary outcomes

The primary outcome measure in this study was local recurrence. A local recurrence was defined as a recurrence of the cancer within the radiation treatment field, either in the treated breast or in the lower part of the axilla. Pathological confirmation with a cytology specimen obtained via needle aspiration or a biopsy was required to document a local recurrence. Whether or not a patient experienced a local recurrence of her disease and, if so when this occurred was ascertained retrospectively at the time of chart abstraction.

Other primary outcomes examined include:

- systemic recurrence, or metastasis, defined as recurrence of the cancer at any site other than the affected breast.
- disease-free survival, defined as survival without local or distant recurrence.
- overall survival.

These outcomes were categorical. Dates of events, such as local recurrence, metastasis and death (due to the breast cancer or other causes), were recorded. With these dates, we defined the total follow-up time from the date of surgery to the date of the first event, or to the date of last visit if the patient was disease-free at that time.

4.3.2 Secondary outcome

The secondary outcome, the waiting time, consisted of the difference in days between two

dates. The first time point was the date of surgery. If the patient had her segmental mastectomy and axillary node dissection on different dates, the date of excision of the primary tumour was used. If needle aspiration or biopsy was performed prior to surgery, or if a re-excision was performed after the segmental mastectomy, the date of the definitive surgical procedure was used as the starting date for the waiting time. The second time point was the date on which the first fraction of radiotherapy was administered. The date of the initial consultation with the radiation oncologist was also recorded in order to examine the various components of the waiting time. With these dates, we defined three intervals: time to radiation treatment, which was from the date of surgery to the date of the first treatment; time to consultation, which was from the date of surgery to the date of the first consultation in the radiation oncology department; and time to treatment unit, which was from the date of the first consultation in the radiation oncology department to the date of the first radiation treatment. Time to radiation treatment was a combination of time to consultation and time to treatment unit.

4.4 Covariates

As previously discussed in the background section, known factors mentioned in the literature may influence the risk of local or distant recurrence of breast cancer and the waiting time for radiation treatment.

4. 4.1 Demographics factors

- Patient age [continuous variable].

4. 4.2 Staging and Pathological Factors

- Disease stage [I or II] as per AJCC recommendations (13), based on pathological findings [categorical variable].

- Tumor grade [1=well, 2=moderately or 3=poorly differentiated] [categorical variable].

- Size of primary tumour in largest dimension as measured in centimetres [continuous variable].

- Number of nodes involved for patients with node-positive disease [continuous variable].

- Proportion of nodes involved for patients with node-positive disease - ratio of the number of positive nodes to the total number of nodes sampled [continuous variable].

- Resection margin status [clear or involved, whether or not the surgical margins showed any tumour at the inked margin of resection] [categorical variable]. The presence or absence of ductal carcinoma in situ (DCIS) in the tumour specimen was not assessed.

4.4.3 Socio-economic factors

- Median income based on the patients' residential postal code [continuous variable]. Median incomes by postal code of residence are published annually by Statistics Canada. Information from the most recent publication was used (55).

4.4.4 Treatment-related factors

- Total dose of adjuvant radiotherapy [50 Gray (Gy), < 50 Gy, > 50 Gy] [continuous variable].

- Number of fractions administered [25, < 25, > 25] [continuous variable].

- Boost given [yes or no] [categorical variable].

- Radiotherapy technique used [breast or breast and ipsilateral axillary nodes] [categorical variable].

- Adjuvant chemotherapy [yes or no]. If yes, then regimen [cyclophosphamide/methotrexate/5-fluorouracil (CMF), with cyclophosphamide administered intravenously (IV) or orally (PO), adriamycin/cyclophosphamide (AC), or other] [categorical variable].

- Tamoxifen therapy [yes or no] [categorical variable].

- On study protocol [yes or no] [categorical variable].

4.4.5 Health care system-related factors

- Referring institution [teaching or nonteaching]: A teaching institution is defined as a facility affiliated with a medical school and/or which has resident physicians providing patient care [categorical variable].

- Radiotherapy centre [nominal variable].

4. 5 Data Collection Methods

Data on the following patient-related variables were obtained by reviewing patient records at each of the institutions providing radiotherapy. The main pathology report was reviewed in order to obtain information, and the pathological evaluations of specimens from surgeries performed at other hospitals were systematically reviewed in our institutions. At all of the institutions, information regarding patients treated with radiotherapy and the indications for

treatment was readily available in the radiation oncology departments. Thus, a list of all women treated with adjuvant radiotherapy for stage I or stage II breast cancer during the study period was obtained from each institution. The patient data sheet used in the study is shown in Appendix A. The demographic data, details regarding tumour pathology and the radiotherapy administered, and information as to subsequent events were available in the radiation oncology chart for most of the patients. Some of the remaining data, such as those concerning treatment with chemotherapy, were recorded only in the hospital chart or in the medical oncology chart.

Thus, for each institution, a plan of action was followed. All of the information was available for approximately 70% of the patients from the radiation oncology records. These were therefore reviewed first. Subsequent measures were taken only if there was missing information. Chart abstraction took 20 minutes per patient. The next step, which was required only for approximately 30% of the patients, was to review the hospital charts. The last step, that of reviewing the medical oncology records, was required only for approximately 10% of the patients. Extraction of the relevant information was performed by me and a trained data abstractor. Problems interpreting the data obtained by the chart abstraction process were discussed. Patients who had not been seen for more than a year were identified as being lost to follow-up.

The database into which the data were to be entered was prepared and adapted for the study before it began. Adequate measures preserving the confidentiality of the data were in place. Both numerical and character data were entered into the spread sheet (Quatropro for Windows) from the data sheets. Values that were out of range or inconsistent with those obtained for other

variables were identified as they were entered. The validity of any outlying data points or inconsistent data was verified by checking the original patient records. All patient information in the database was coded by number, and the codes linking the patients' names to their code numbers were stored in a locked filing cabinet.

4. 6 Statistical Analysis

The statistical analysis was performed by a statistician. I supervised the analysis, and I was responsible for interpreting the output. The statistical program used was S+, version 4.0.

4.6.1 Descriptive statistics

The results of the study in terms of patient outcomes, waiting times, and all the covariates were reported using descriptive statistics such as the mean and median values, as well as the ranges and standard deviations of the values obtained. The 95% confidence intervals (CIs) were obtained for the appropriate parameters. The mean overall waiting time as well as the means of its various components were determined.

4.6.2 Determinants of primary outcomes

The categorical dependent variables were the patient outcomes, i.e local recurrence, systemic recurrence and disease-free survival. The main exposure was time to radiation treatment, which could be split into time to consultation and time to treatment unit. The relationship between time to radiation treatment, which was treated as a continuous variable, all the potentially important covariates and confounders and the primary outcome measure, the local recurrence rate,

was first determined by means of univariate analysis using regression models. The covariates were the demographic, staging, pathological, socioeconomic and treatment-related factors. All covariates for which there were *a priori* strong clinical reasons for a relationship and all those with a statistically relevant influence on the local recurrence rate were entered into a Cox proportional hazards model along with time to radiation treatment (58). Continuous variables that were highly skewed, such as time to radiation treatment, were subjected to log transformation. The suspected confounding factors were the use and nonuse of chemotherapy. Therefore, a correlation matrix was created for all the patients and subsequently for the chemotherapy group and the nonchemotherapy group for different factors such as age, income, tumor size and time to radiation treatment.

The effect of time to radiation treatment on the local recurrence rate was determined following adjustments made to correct for differences between patients with regard to other important prognostic factors. Thus, the true impact of increases in delay prior to commencing adjuvant radiotherapy for women with early-stage breast cancer was ascertained. In addition, the covariates with independent effects on the local recurrence rate were identified. Furthermore, the parameter estimates for the independent predictors are easily interpretable as relative risks, either with respect to a baseline (categorical or discrete variables) or per unit of change (continuous).

4.6.3 Determinants of secondary outcomes

The dependent variable was time to radiation treatment, which was split into time to consultation and time to treatment unit. The main exposure was among the various patient-related

and health-care system-related factors. Similarly, the relationship between time to radiation treatment, which was treated as a continuous variable, and all the potentially important covariates and confounders was first determined in a univariate analysis using regression models. The suspected confounding factors were the use or nonuse of chemotherapy and the type of chemotherapy. Continuous variables that were highly skewed, such as time to radiation treatment, were subjected to log transformation. All covariates for which there were *a priori* strong clinical reasons for a relationship and all those with a statistically relevant influence on the waiting times were entered into a Cox proportional hazards model (58). Using this information, the anticipated effects associated with varying alterable factors on time to radiation treatment were examined.

4.6.4 Modelling Strategy

In addition, to identify changes in continuous predictive variables that may not exist, such as time to radiation treatment, we employed an exploratory data analysis tool called "recursive partitioning" (59). This method starts with the complete sample population and searches among all the available predictors to find the variable which, when partitioned, maximizes the differences in the a-priori defined model criteria. In our case, we maximized the value of the Cox likelihood ratio. Once a split or partitioning is achieved, the process repeats itself, factoring in all the previous splits, hence the term "recursive". The results of this analysis are represented as a binary tree. Thus, this method reveals optimal cut-off points for each of the candidate predictor variables.

Lastly, we reintroduced the predictor variables identified by the recursive partitioning analysis as dummy variables into the Cox regression model along with all the previously defined

variables that had not been entered into the recursive partitioning model, and we confirmed the significance of the previously defined variables.

5. Results

5.1 Clinical findings

The patient characteristics are reported in Table 2. The median age of our population was 59 years. Of these women, 58% had a stage I tumour, with a median tumour size of 1.5 cm, and 38% had a histological grade 2 tumour. The majority of these patients (73%) were referred by a university hospital. Twenty-eight per cent of them received adjuvant chemotherapy, and 53% received tamoxifen, but only 26% were treated according to protocol. Their estimated median income was $ 24, 650 CDN .

Most of the patients received radiation treatment to the chest wall with two tangential fields (N=457). The others were treated with the McGill technique to the chest wall and the regional lymph nodes (N=29). Only three patients were reported to have a positive margin, and 21 received a boost. Most of the women received 50 Gy in 25 fractions (N=473), 5 received 45 Gy in 20 fractions and 8 received up to 55 Gy in 27 or 28 fractions.

As might be expected, differences were observed between the patients who received chemotherapy (N=137) and those who did not (N= 349). Those who did were younger (median age of 50 years compared to 60), tended to have larger tumours (median size of 1.96 cm compared

to 1.65), which were consequently more often stage II (62% compared to 34%), and presented with higher-grade tumours (47% had grade 3 compared to 20%). The median income and the referring hospital distribution pattern were similar in both groups.

For the entire population, the median time to radiation treatment was 56 days, with a median time to consultation of 31 days and a median time to treatment unit of 25 days.

5.2 Primary outcomes

At 5 years, 34 patients (7 %) were lost to follow-up. The median follow-up was approximatively 70 months. Fifty-two patients died of their breast cancer. The 5-year disease-free survival rate was 89% (Fig. 1), the 5-year local recurrence rate 8% (Fig. 2) and the 5-year metastatic rate 13% (Fig. 3). Forty patients developed a local recurrence, 35 in the treated breast and 5 in the lower axilla at a median follow-up time of 36 months. Sixty-two patients had distant metastases at a median follow-up time of 30 months, and nine of them developed both local recurrence and metastases.

5.3 Prognostic factors of primary outcomes

5.3.1 Univariate analysis

Our initial descriptive analysis is as follow:

No correlation was found between the variables, especially between time to radiation treatment and use of chemotherapy, or between time to radiation treatment and age, income or tumor size. Table 3 provides statistics stratified by development of local recurrence. Patients who

developed a local recurrence were younger (50 compared to 58 years), had a higher histological grade (grade 1 compared to grade 2 and 3) and waited longer for their radiation treatment (mean of 95 compared to 71 days). All the CI limits for the between-group differences were above zero and were clinically important. Stage and tumour size, referring hospital and income did not have a significant impact on the local recurrence rate, with the CI for the between-group differences including zero. The adjuvant treatment modalities, such as tamoxifen or chemotherapy, could have an impact on the risk of local recurrence, with the CI for the between-group difference excluding zero: 55% and 27% of the patients without local recurrence received, respectively, tamoxifen or chemotherapy compared to 35% and 45% of those with local recurrence. This information is clinically important for tamoxifen, since it indicates that hormonotherapy could decrease the risk of local recurrence, but not for chemotherapy. Consequently, no conclusion could be drawn. Further study is required to determine the magnitude of this factor. For the patients who developed a local recurrence, the 95 days of time to radiation treatment was a combination of 48 days of time to consultation and 47 days of time to treatment unit. For the patients with no local recurrence, the 71 days of time to radiation treatment was a combination of 40 days of time to consultation and 31 days of time to treatment unit.

Table 4 summarizes the clinical and demographic characteristics of the patients who survived and of those who died of their breast cancer. No difference in patient characteristics was observed between the two groups for age, stage, tumour size, adjuvant treatment modalities, referring hospital, income or time to radiation treatment. The only difference concerned the histological grade: patients with grade 2 or 3 had a worse 5-year survival rate than the patients

with histological grade 1 (CI for the between-group difference above zero). Time to radiation was 70 days for the patients who died and 74 days for those who survived. Interestingly, the percentage of patients who received chemotherapy was similar between the two groups: 28% in the surviving group and 34% in the nonsurviving group.

Table 5 compares the prognostic factors between patients with and without metastatic events. The patients with metastatic disease (N=52) were younger (53 compared to 58 years), had a higher histological grade (1 compared to 2 and 3) and were more likely stage II. Adjuvant treatment modalities, referring hospital and income did not have a significant impact on the risk of metastases (CI for the between-group difference included zero). Time to radiation treatment did not influence the risk of metastatic events. It was 75 days for the metastatic group and 73 days for the nonmetastatic group.

5.3.2 Multivariate analysis

Table 6 indicates the importance of each variable in the multivariate Cox survival regression model. With local recurrence as an outcome, both grade (2 and 3 as opposed to 1) and time to radiation treatment yielded statistically significant values. The information provided by the CI for the RR was of clinical interest. Over the 5-year period, a patient delayed by one unit of time in log scale, representing 93 calendar days from the median, or 148 calendar days in terms of time to radiation treatment, was 2.13 times more likely to suffer a recurrence, while patients with a histological grade 3 tumour were 1.47 times more likely to experience a recurrence than those with a grade 1 tumour. In this series, 27 patients had to wait 148 days or more and 5 local

recurrences occured in this group of patients. The CIs for the RRs for the other variables, such as age, income, treatment modalities and referring hospital, were not revealing.

Considering survival as an outcome, only histological grade 3 compared to grade 1 showed some effect, with an RR of 1.39. Lastly, using metastasis as an outcome, variables such as age (younger than 40, with an RR of 0.54, or older than 60, with an RR of 0.73) and higher histological grade (2 and 3 as opposed to 1, with, respectively, an RR of 1.51 and 1.25) showed some effect. The information provided by the 95% CI limits was clinically relevant for grade but not for age, especially the over-60 group. Further study will be required to determine the effect of age.

In the last model (Table 7), the variables were selected according to their clinical relevance and the results of the previous analysis. Time to radiation treatment remained a prognostic factor for the risk of local recurrence (RR=1.87). High histological grade was a prognostic factor for the risk of local recurrence and metastases and for survival. Age as a continuous variable was found to have some impact on the risk of local recurrence (RR=0.67).

5.3.3 Recursive partitioning analysis

Figure 4 depicts the results of the recursive partitioning model using time to local recurrence as the outcome of interest. Starting with the entire patient cohort (n=486), the model pointed to time to radiation treatment as the variable which provided the best discrimination with respect to the local recurrence of breast cancer. The first branch (stratum 1) identifies 117 patients

(24%) who waited 79 days (delay given by the model) or more before starting radiation therapy. For these patients, the average time to radiation treatment was 143 days, with a mean time to consultation of 80 days (SD=78, range=0-168) and a mean time to treatment unit of 63 days (SD=50, range=13-113). These patients were almost five times more likely to suffer recurrence than those treated within 79 days from their surgery, adjusting for the length of follow-up. For the patients treated within 79 days, the average time to radiation treatment was 51 days, with a mean time to consultation of 28 days (SD=11, range=17-39) and a mean time to treatment unit of 23 days (SD=10, range=13-33). The next branch (stratum 2), proceeding from left to right, classifies the patients who received treatment within 79 days and who had grade 3 tumours. The last branch (stratum 3) shows the patients treated within 79 days who had either grade 1 or 2 tumours. Using stratum 1 as the baseline, the relative risk (RR) of local recurrence was 0.46 in stratum 2 and 0.15 in stratum 3. Thus, patients with delayed treatment were more than twice as likely to suffer recurrence than those for whom there was no delay. However, having a grade 3 tumour put patients at more than a 6-fold greater risk than the patients for whom treatment was not delayed and who had a grade 1 or 2 tumour. Further splits were difficult due to the sample size.

The probability of no local recurrence in each stratum over time is reported in Figure 5. The difference between strata increased gradually. At five years, the probability of local recurrence in patients who received their radiation treatment 79 days or more after their surgery (stratum 1) was 20.5%, whereas it was 8.5% for those who were treated within 79 days and who had grade 2 or 3 tumours (stratum 2), and 3% for those who were treated within 79 days and who had grade 1 tumours (stratum 3).

Furthermore, we substituted the three strata into a Cox regression along with all the previously described covariates. The dependent variable was the local control rate. The main exposures were stratum 1 (delay of 79 days or more in radiation treatment) and stratum 2 (delay of less than 79 days, grade 2 or 3) compared to stratum 3 (delay of less than 79 days, grade 1). The covariates were the demographic factors, the staging and pathology, and the socioeconomic and treatment-related factors. No other variables or combination of variables significantly improved the fit of the model conditioned on the prognostic strata as derived from the recursive partitioning model.

5.4. Prognostic factors of secondary outcome

Analyses were performed using a multivariate Cox survival model with time to radiation treatment as the principal outcome and stratification by use or nonuse of chemotherapy. In the first analysis, time to radiation treatment, which was a continuous, skewed variable, was subjected to log transformation. In this model, for the chemotherapy group, only stage of disease (95% CI=0.06 to 0.42) and being treated on protocol (95% C =-0.62 to -0.24) had an impact on time to radiation treatment: patients with stage II and those on protocol waited less to receive their radiotherapy. For the nonchemotherapy group, only the fact of receiving adjuvant tamoxifen (95% CI=-0.20 to -0.012) had an impact on time to radiation treatment, with patients on tamoxifen waiting less for their irradiation.

The second analysis was performed using the information obtained from the recursive

partitioning model. Acceptable delay, or the reference value, was defined as time to radiation treatment of less than 79 days, excessive delay as time to radiation treatment of 79 days or more. In this model, for the chemotherapy group, stage of disease (95% CI=-2.6 to -0.8) and being treated on protocol (95% CI=0.61 to 2.18) had an impact on time to radiation treatment. The results obtained for the variable of tumour size were inconclusive (95% CI=0 to 0.94). The patients with stage II (OR=0.17) and those treated on protocol (OR= 4) waited less for their radiation treatment. For the nonchemotherapy group, only the stage of disease (95% CI=-2 to -0.42) was associated with time to radiation treatment. The patients with stage II disease (OR=0.28) waited less than those with stage I disease.

6. Discussion

6.1. Limitations of the study

The strongest study design for testing the hypothesis that increased waiting times for adjuvant radiotherapy increase the risk of local recurrence of breast cancer would be a randomized clinical trial. However, it would clearly be unethical to randomize patients to short or long waiting times, given data from the literature suggesting that longer waiting times may be detrimental to patient outcomes. A prospective cohort study comparing the outcomes of women with various durations of delay prior to receiving adjuvant radiotherapy could be an another alternative. It would minimize loss to follow-up, permit the collection of all relevant information, and alleviate concerns about the accuracy of the data obtained. However, a prospective study would have two major drawbacks. First, the study would take at least six years to complete in

order for it to provide a median duration of follow-up similar to that in the proposed study. Second, it would be much more expensive than our study and would not provide much additional benefit. By utilizing a retrospective design, our study was carried out at a lower cost, with results that are valid and reliable because of nearly complete follow-up (7% lost to follow up) and appropriate data handling. Though an effort was made to obtain follow-up information on all of the study patients, some patients sought medical care at institutions not involved in the study or moved out of the province of Quebec.

Lastly, confounding can bias the results of retrospective studies. In order to minimize the effects of confounders in our proposed study, data on a large number of known and suspected prognostic factors from the literature were obtained, and the influence of these covariates on the outcome measures was controlled for in the analysis. There can be problems with the accuracy of data obtained in a retrospective fashion through the utilization of hospital records. However, with the collection of data by only two abstractors, strict adherence to standard criteria documenting events, and the systematic discussion of all problems, we tried to minimize this problem.

Some other potential limitations of our study need to be discussed. The original pathology was not reviewed to assess the margins of excision or to verify the presence of an extensive intraductal component. Clear margins were defined as no malignant cells at the cut surface on microscopic examination, but no minimum width was required, as stipulated in the National Surgical Adjuvant Breast Project (NSABP) recommendations (2). We relied on the pathological evaluation performed at our institutions, which systematically reviewed pathology specimens for

surgeries performed at other hospitals. Furthermore, all patients with positive margins were systematically managed with surgical re-excision to obtain negative margins or by delivering a 10-Gy boost to the tumour bed. The presence of extensive ductal carcinoma in situ was not extracted from the pathological report, since this information was not systematically reported in the charts. Therefore, the pathological assessment and the management of positive margins were similar for all cases, whether patients waited or not for their radiation treatment. This resulted in a random misclassification. Reported delays included those for patients who did and did not receive chemotherapy. Chemotherapy was a potential confounding factor: the patients who received chemotherapy were delayed in receiving their irradiation, especially if they received anthracycline-based chemotherapy, and chemotherapy could decrease the risk of local recurrence. However, in our study, no correlation was found between time to radiation treatment and use of chemotherapy. Also, in the univariate analysis of the risk of local recurrence, the information on chemotherapy was inconclusive. Therefore, we believe that we can report the impact of delay on the risk of local recurrence for both patient groups combined.

6.2. Achievement of primary objective

Our analysis of stage I and II breast cancer patients treated with conservative surgery followed by radiation therapy showed a local recurrence rate of 8%, a metastasis rate of 13% and a disease-specific survival of 89% at five years. This is consistent with results reported in the literature (2,6).

Time to radiation treatment, defined as the interval between the date of surgery and the

date of first radiation treatment, had a significant impact on the risk of local recurrence in the univariate and multivariate analyses. Adjusting simultaneously for age, tumour size, grade, referring hospital, income and protocol, patients who waited 79 days or more prior to treatment of radiation therapy were almost five times more likely to suffer a local recurrence than those treated within 79 days of their surgery. Furthermore, the patients who waited 79 days or more (11 weeks) had a 20.5% risk of local recurrence at 5 years, while patients treated with lumpectomy alone without adjuvant irradiation have been reported to have a 35% risk of local recurrence at 12.5 years (2). Therefore, a delay of 11 weeks or more after the initial surgery tends to reduce by approximatively one half (from 27% to 14.5%) the benefit of postoperative radiation in terms of the local recurrence rate. The waiting time for radiation therapy did not influence the risk of distant metastasis or the survival rate at 5 years.

These results are consistent with those of the literature review provided in Table 1. The cut-off point of 79 days for time to radiation treatment reported in our study falls within the 75 to 180 days with respect to which most of the authors reported that delay had an impact on the risk of local recurrence.

6.3. Achievement of secondary objectives

6.3.1. Predictors of local recurrence (other than waiting time)

Among the patient-related variables, histological grade was a significant prognostic factor for the risk of local recurrence. Histological grade 3 tumours involve a higher risk of local recurrence, the development of metastases and worse survival than grade 1 tumours. Patients with

histological grade 3 tumours were 1.47 times more likely to develop a local recurrence than those with grade 1 tumours. Furthermore, the patients who received their irradiation within 79 days of their surgery and who had histological grade 3 tumours were at three times greater risk than the patients whose radiation treatment was not delayed and who had grade 1 or 2 tumours. Other variables, such as age, stage, tumour size, referring hospital, being on adjuvant treatment or treated on protocol, did not have a significant impact on the risk of local recurrence. Income did not influence these patients' outcomes either (narrow CI). However, a patient's residential postal code as a surrogate for her income was clearly only an approximate indicator, given the wide range of incomes within a given postal code area, but it is commonly accepted in the literature.

Our results were consistent with the data reported in the literature (see background section). Poor histological grade tumours were associated with worse outcomes. Only three patients in our population had a positive margin. Consequently, gross margin involvement could not be associated with the risk of local recurrence. Lastly, young age and large tumour size were not found to be associated with an increased risk of local recurrence.

6.3.2. Predictors of waiting time

For the patients who received chemotherapy, time to radiation treatment was associated with stage of disease and being treated on protocol. The patients with stage II disease and those on protocol waited less to receive their radiotherapy. For the patients who did not receive chemotherapy, time to radiation treatment was associated with tamoxifen use and possibly stage of disease: patients on tamoxifen and with stage II disease waited less for their irradiation.

Predictors similar to those revealed by our previous analysis of the predictors of delay in starting radiation treatment for patients with early breast cancer were found for the patients who received chemotherapy, such as stage and being on a study protocol, but not for those treated without chemotherapy (54). In particular, referring hospital was not found to have an impact on time to radiation treatment. Again, income was not shown to be a predictor of delay, as lower-income patients did not wait longer for radiation treatment than higher-income patients. As in the literature examining waiting times for radiation treatment, age was not associated with delayed treatment in our analysis. No correlation was found between time to radiation treatment and age. However, it is possible that older patients underwent radical mastectomy more often than conservative treatment and were therefore never referred for adjuvant radiation treatment. The National Cancer Policy Board recently issued a report stating that only 24% of all women with breast cancer over the age of 80 in the United States receive the radiation treatment required after a lumpectomy. In our study, delays due to postoperative complications were not tracked. Nor was the information on the equipment and staff level as regards the departmental workload. All of this information will need to be collected to complete the evaluation of factors influencing time to radiation treatment. Lastly, "channelling bias" could explain why stage II patients were treated sooner than stage I patients: patients with a worse prognosis may have been referred more quickly by the referring physician and may have also been started on therapy sooner at the treatment unit.

6. 4. Importance of the study

Our study confirmed the importance of radiation treatment after breast-conserving surgery as a means of local control of the disease. It showed that delivering radiation treatment as soon as

possible after surgery reduces the likelihood of local recurrence. The use of modelling enabled us to determine a clinically relevant cut-off point: a delay of more than 79 days (11 weeks) after surgical treatment in starting radiation therapy was associated with a higher risk of local recurrence. This data will need to be verified in a larger study in order to define what an "acceptable" waiting time is for radiation treatment, knowing that a larger proportion of patients with early-stage disease are now receiving adjuvant chemotherapy.

6.4.1 Impact of local recurrence on survival

Achieving local control of the disease is important, but improving survival is even more so. In theory, knowing that excessive time to radiation treatment is associated with an increased risk of local recurrence and that local recurrence may lead to further dissemination of cancer cells and to an increased risk of metastasis, a decreased overall survival rate could be expected (5, 31). In our study, at 5 years of follow-up, delay in radiation treatment did not have any impact on survival.

A study in which patients with stage I or II breast cancer were randomly assigned to receive a 12-week course of chemotherapy either before or after radiation therapy showed that, at 5 years of follow-up, local recurrence was more common when radiation therapy was given after completion of chemotherapy and that systemic recurrence was more frequent when chemotherapy followed radiation therapy (45). Overall survival was similar in both groups. The authors recommended giving 12 weeks of chemotherapy before irradiation for patients at substantial risk for systemic disease. However, they recommended that these results not be extrapolated to

regimens with more prolonged intervals between surgery and radiotherapy. At 10 years of follow-up, Cowen et al reported that the risk of relapsing with distant metastases was 4.4 times higher after a local recurrence and that the median time to distant metastases was shorter after a local recurrence (5). Fortin et al reported that local failure was associated with an increase in mortality at 10 years of follow-up (60). The relative risk associated with local failure was 3.6 for mortality and 5.1 for distant metastases. In the patients with local failure, the rate of distant metastases peaked at 5 years, whereas it peaked at 2 years for patients with local control of the primary tumour. Veronesi et al showed that local recurrence and distant metastases were partially independent events (61). Women 35 years old or younger at first diagnosis who had local recurrence within 2 years and an initial peritumoral lymphatic invasion were at high risk of distant spread. However, women who had local recurrence with an extensive intraductal component or an inadequate initial local surgery were at lower risk of distant spread. Lastly, at 10 and 15 years of follow-up, Ragaz et al and Overgaad et al showed that postoperative irradiation not only decreases local recurrence rates but prolongs survival as well (62,63). Therefore, in line with the Canadian guidelines for the care and treatment of breast cancer, we can confirm that radiation therapy should be given as soon as possible after surgery in patients who did not receive chemotherapy. For patients at higher risk for systemic disease and in whom the combined approach is used, the optimal schedule has not yet been defined. However, given our results, we recommend that radiation treatment not be delayed for more than 11 weeks.

With the combination of chemotherapy and irradiation, another factor has to be taken into account: the increased likelihood of acute and late normal tissue damage. Bentzen et al showed

with CMF chemotherapy an increase in the risk of developing moderate and severe subcutaneous fibrosis after postmastectomy radiotherapy (64). We would need to review our experience at McGill, which involved the combined use of CMF chemotherapy and irradiation, as regards long term toxicity. With anthracycline-based chemotherapy, irradiation is systematically given after the completion of 4 cycles of chemotherapy, and this could be done before the 11-week cut-off point. However, new studies exploring novel agents that might permit radiation therapy to be delayed even longer are underway. The NSABP proposed a study in which patients were randomized to receive postoperatively 4 cycles of AC, which were or were not followed by 4 cycles of taxol. Irradiation was given after the completion of chemotherapy, that is 12 or 24 weeks after surgery. With sufficient follow-up, this study will provide information about local control and survival rates that will make it possible to determine the best timing for radiation treatment when it is combined with chemotherapy.

6.4.2 Impact of local recurrence on patient

Furthermore, the time spent waiting to receive treatment for an already traumatic condition could constitute an additional source of anxiety for these women and significantly affect their quality of life. Studies have found that psychological factors are important contributors to a person's health and quality of life (65). The addition of delay-related anxiety to the already well-documented illness-related anxiety which has been associated with breast cancer could be detrimental to the patient's well-being. However, there is no clinically relevant standardized assessment scales appropriate for use in a breast cancer population with regard to waiting times for radiation treatment. Research on the measurement of anxiety and other mood states

experienced by breast cancer patients and that are specifically related to this waiting should be undertaken.

6.4.3 Impact of local recurrence on health care system

Lastly, the cost to society associated with the delays in radiation treatment should be assessed. Waiting for radiation therapy is still a daily reality in the Canadian health care system. In our institution, we observed that the median time to the treatment unit has increased over the past decade. It was 25 days in the late 1980s and 35 days in the early 1990s (54). In 1996, health-care reforms were initiated in Canada. The results of a recent survey showed that Canadians are now waiting even longer to receive medical care, including radiation treatment (10). The health-care reforms were aimed at reducing the cost to society and resulted in a major drop in public health expenditures.

In Quebec, the restructuring of the health-care system was marked by the "virage ambulatoire" (increase in ambulatory care services), cuts in hospital budgets, hospital mergers, and early retirement incentives to reduce the number of physicians, nurses and technologists. Radiation oncology departments, which are regionalized structures, were strongly affected by the budgets cuts. From the survey of all Canadian centers that provided radiotherapy services in 1997 it appears that there is a significant amount of between-province variation in staff workload for the main professionals in radiotherapy, such as radiation oncologists, radiotherapists, clinical physicists and radiation dosimetrists (52). For instance, Quebec, with 25% of all patients treated in Canada, exceeded the national staff workload averages for all four of these professional groups

but was in compliance with the national radiotherapy equipment levels. Therefore, it would be important to describe how the provision of resources pertaining to radiation therapy equipment and personnel has changed over the past decade and to develop a model to describe how delay in treatment is related to the provision of resources. This is particularly important, since we expect an increase in the incidence of breast cancer in the coming years. The province of Quebec has started a screening program in which all women over the age of 50 will be advised to have a mammogram. Furthermore, breast cancer classically occurs after menopause, and babyboomers are now turning fifty. Therefore, a peak in the number of patients with early-stage breast cancer, who will be treated conservatively and require adjuvant irradiation, can be expected.

Furthermore, once a local recurrence has been diagnosed, further treatment is necessary. Usually, further tests are ordered: a biopsy to confirm the recurrence and a complete work-up, including a bone scan, an abdominal ultrasound and chest X-rays to rule out any distant disease. Then treatment is performed, surgery when possible, with or without systemic treatment and radiation therapy. All these procedures generate costs and have an economic impact, such as time off from work for patients who are professionally active. Therefore, a cost-effectiveness analysis should be performed that examines the costs generated by a local recurrence, including human factors and the resources necessary to reach the recommended staff and equipment levels.

7. Conclusion

For stage I and II breast cancers, delay in radiation treatment is an important determinant of local recurrence. Adjuvant radiation treatment should be delivered as soon as possible after conservative surgery, even when patients receive combined treatment with chemotherapy and irradiation. However, guidelines also need to be established to determine the choice of treatment between radiation therapy and chemotherapy in light of the severity of the patient's condition. Longer follow-up is necessary to assess the impact of delay on survival.

We believe that the results of this study will contribute to the current debates on access to essential health-care services. Health-care policies should be established to reduce waiting lists in radiation oncology departments, to optimize this therapeutic modality and to serve patients.

List of Tables

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Table 1: Literature review of impact of delay in radiation therapy in patients with early breast cancer

Author (ref)	N/FU	Treatment RT (boost)/CT	Impact of delay on LR (% pts with delay)	Comments
Clarke (36)	436/ 60	45 (15)/no	Yes if D > 49 d (13 %)	In univariate analysis
Whelan (37)	400/100	40 (12.5)/no	Trend if D > 56 d (46%)	
Nixon (40)	653/100	45 (15)/no	No if D up to 56 d (8%)	No data for D> 56 d
Fourquet (41)	1839/78	50 (15)/no	No if D up to 56 d (3%)	No data for D > 56 d
Slotman (39)	514/68	50 (15)/no	Yes if D > 75 d (6%)	
Recht (44)	295/78	45 (16)/yes	Yes if D > 112 d (12%)	
Vujovic (42)	568/63.5	50(+/-10)/ no	No if D up to 112 d (7%)	Impact of boost?
Recht (45)	244/58	45 (16)/yes-no	Yes if D > 116 d (50%)	Prospective study
Buccholz (43)	105/96	45 (15)/yes	Yes if D > 180 d (54%)	Impact on survival

N: number of patients; FU: follow-up in months; RT (boost): dose of radiation given including boost; CT: chemotherapy; LR: local recurrence; D: delay in days.

Table 2: Patient characteristics

	Total	No chemotherapy	chemotherapy
Number	**486**	**349**	**137**
Median age, years (SD) (range)*	59	60 (10.6) (49.5 to 70.7)	50 (10.9) (38.8 to 60.6)
Stage I (%)	58	66	38
Stage II (%) *	42	34	62
Median tumour size, cm (SD) (range)	1.5	1.65 (0.86) (0.79 to 2.51)	1.96 (0.9) (1.06 to 2.86)
Grade 1 (%)	27	35	18
Grade 2 (%)	38	45	53
Grade 3 (%) *	25	20	47
Tamoxifen (%)	53	65	23
On protocol (%)	26	18	46
Community hospital (%)	27	28	23
University hospital (%)	73	71	76
Median income ($ CDN)	24, 650	25, 235	24, 698

*statistical differences between groups at the 0.05 level

SD: standard deviation, cm: centimeters, $ CDN: Canadian dollars

Table 3: Univariate analysis of prognostic factors for local recurrence

	No recurrence (N=446)	Recurrence (N=40)	95% CI
Median age, years (SD) * (range)	58 (0.55) (57.4 to 58.5)	50 (1.65) (48.3 to 51.65)	3.95 to 10.99
Stage I (%)	59	53	-11 to 24
Median tumour size, cm (SD) (range)	1.75 (0.04) (1.71 to 1.79)	1.66 (0.14) (1.52 to 1.8)	-0.21 to 0.38
Grade 1 (%)*	32	13	6 to 32
With chemotherapy (%)	27	45	-36 to -1
Tamoxifen (%)	55	35	3 to 37
On protocol (%)	27	18	-4 to 23
University hospital (%)	72	85	-26 to 0.1
Income, $ CDN (SD) (range)	24, 940 (361) (24, 579 to 25, 301)	23, 800 (999) (22, 801 to 24, 799)	-987 to 3, 280
Time to radiation treatment, days (SD) (range) *	71 (2.81) (68, 74)	95 (6.32) (89, 101)	-38 to -9.2

*Statistical differences between groups at the 0.05 level

SD: standard deviation; CI: confidence interval for the between-group difference;

cm: centimeters, $ CDN: Canadian dollars

Table 4: Univariate analysis of prognostic factors of survival

	Alive (n= 434)	Dead (n=52)	95% CI
Median age, years (range)	57 (56.4 to 57.5)	57 (55.3 to 58.6)	-3.8 to 3.2
Stage I (%)	50	59	-6 to 25
Median tumor size, cm (range)	1.73 (1.69 to 1.77)	1.79 (1.69 to 1.87)	-0.14 to 0.25
Grade 1 (%) *	27	18	2 to 27
Chemotherapy (%)	28	34	-20 to 9
Tamoxifen (%)	53	61	-24 to 6
On protocol (%)	27	21	-7 to 18
University hospital (%)	72	80	-21 to 5
Income, $ CDN (range)	25,110 (24,751 to 25,469)	22,660 (21,610 to 23,710)	-4,666 to -230
Time to radiation, days (range)	74 (71 to 76.9)	70 (64.7 to 75.2)	-16 to 8

* Statistical significance between groups at the 0.05 level

CI: confidence interval for the between-group difference; cm: centimeters; $ CDN: Canadian dollars

Table 5: Univariate analysis of factors prognostic of metastases.

	No metastases (N=424)	Metastases (N=62)	95% CI
Median age, years (range) *	58 (57.4 to 58.5)	53 (51.4 to 54.5)	1.03 to 7.55
Median tumor size, cm (range)	1.69 (1.65 to 1.73)	2.07 (1.96 to 2.18)	-0.6 to -0.14
Stage I (%) *	62	37	11 to 38
Grade 1 (%)*	10	34	13 to 33
Chemotherapy (%)	26	42	-30 to -2
Tamoxifen (%)	53	60	-21 to 7
On protocol (%)	24	27	-10 to 15
University hospital (%)	72	77	-17 to 8
Income, $ CDN (range)	25,040 (24,677 to 25,403)	23,560 (22,571 to 24,549)	-615 to 3,580
Time to radiation, days (range)	73 (70 to 75.9)	75 (69.6 to 80.3)	-14 to 10

* Statistical significance between groups at the 0.05 level

CI: confidence interval for the between-group difference; cm: centimeters; $ CDN: Canadian dollars

Table 6: Multivariate analysis of prognostic factors

	Survival: RR (95% CI)	Local recurrence: RR (95% CI)	Metastases: RR (95% CI)
30-40 years	0.65 (0.37 to 1.14)	0.9 (0.56 to 1.46)	0.54 (0.34 to 0.86) *
40-50 years	1 (0.74 to 1.35)	0.93 (0.70 to 1.25)	0.91 (0.71 to 1.17)
50-60 years	1.1 (0.93 to 1.31)	0.8 (0.71 to 1.10)	0.99 (0.85 to 1.16)
> 60 years	1 (0.84 to 1.20)	0.27 (0.004 to 17.39)	0.73 (0.55 to 0.98) *
Tumour size	0.97 (0.64 to 1.46)	0.78 (0.49 to 1.23)	1.17 (0.83 to 1.64)
Stage II/I	0.95 (0.46 to 1.94)	0.89 (0.38 to 2.07)	1.51 (0.76 to 2.99)
Grade 2/1	1.29 (0.86 to 1.94)	1.36 (0.80 to 2.31)	1.51 (1.02 to 2.55) *
Grade 3/1	1.39 (1.12 to 1.72) *	1.47 (1.13 to 1.90) *	1.25 (1.00 to 1.55) *
Tamoxifen	1.51 (0.76 to 2.98)	0.59 (0.19 to 1.11)	1.87 (0.96 to 3.47)
On protocol	0.49 (0.23 to 1.04)	0.46 (0.19 to 1.11)	0.63 (0.3 to 0.96)
University H.	1.54 (0.74 to 3.19)	2 (0.80 to 5.0)	1.36 (0.72 to 2.55)
Income	0.56 (0.25 to 1.29)	0.75 (0.33 to 1.71)	0.62 (0.29 to 1.35)
Time to RT	0.82 (0.47 to 1.44)	2.13 (1.10 to 4.11) *	0.81 (0.50 to 1.31)

* statistical significance between groups at the 0.05 level

RR: relative risk; University H.: University hospital/ reference category: Non-university hospital;

Income in $ CDN; Time to RT: time to radiation treatment in days, with log transformation

Table 7: Multivariate analysis of prognostic factors (model 2)

	Survival: RR (95% CI)	Local recurrence: RR (95% CI)	Metastases : RR (95% CI)
Age		0.67 (0.38 to 0.96)	0.80 (0.34 to 1.28)
Grade 2/1	1.36 (0.97 to 1.78)	1.25 (0.73 to 1.77)	1.81 (1.37 to 2.25)*
Grade 3/1	1.37 (1.17 to 1.57)*	1.44 (1.2 to 1.68)*	1.33 (1.13 to 1.53)*
Tamoxifen			1.91 (1.32 to 2.5)
Time to RT		1.87 (1.38 to 2.36)*	

* statistical significance between groups at the 0.05 level

RR: relative risk; Time to RT: time to radiation treatment in days, with log transformation.

Figure 1

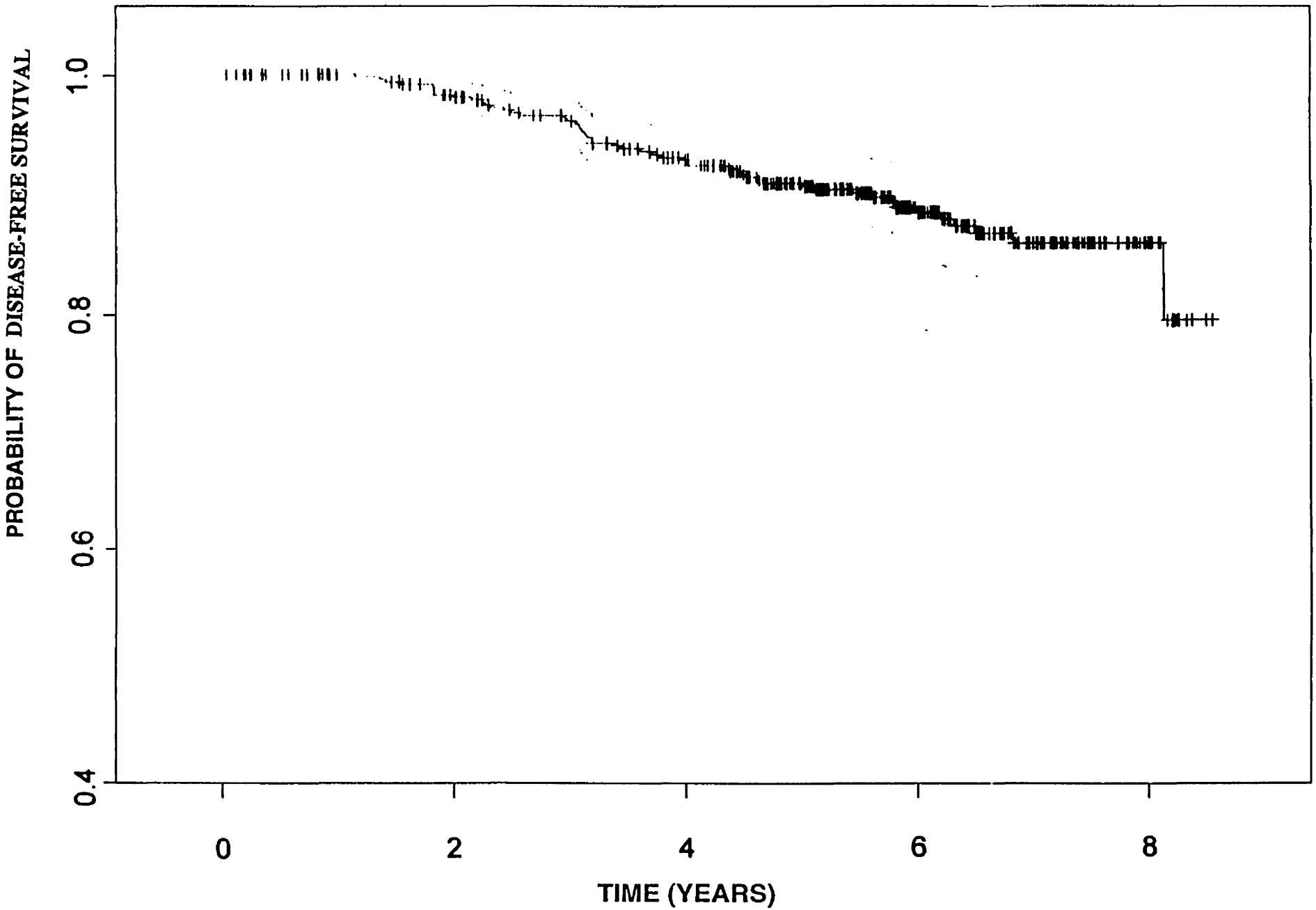

PROBABILITY OF DISEASE-FREE SURVIVAL
1.0
0.8
0.6
0.4
0
2
4
6
8
TIME (YEARS)

Figure 2

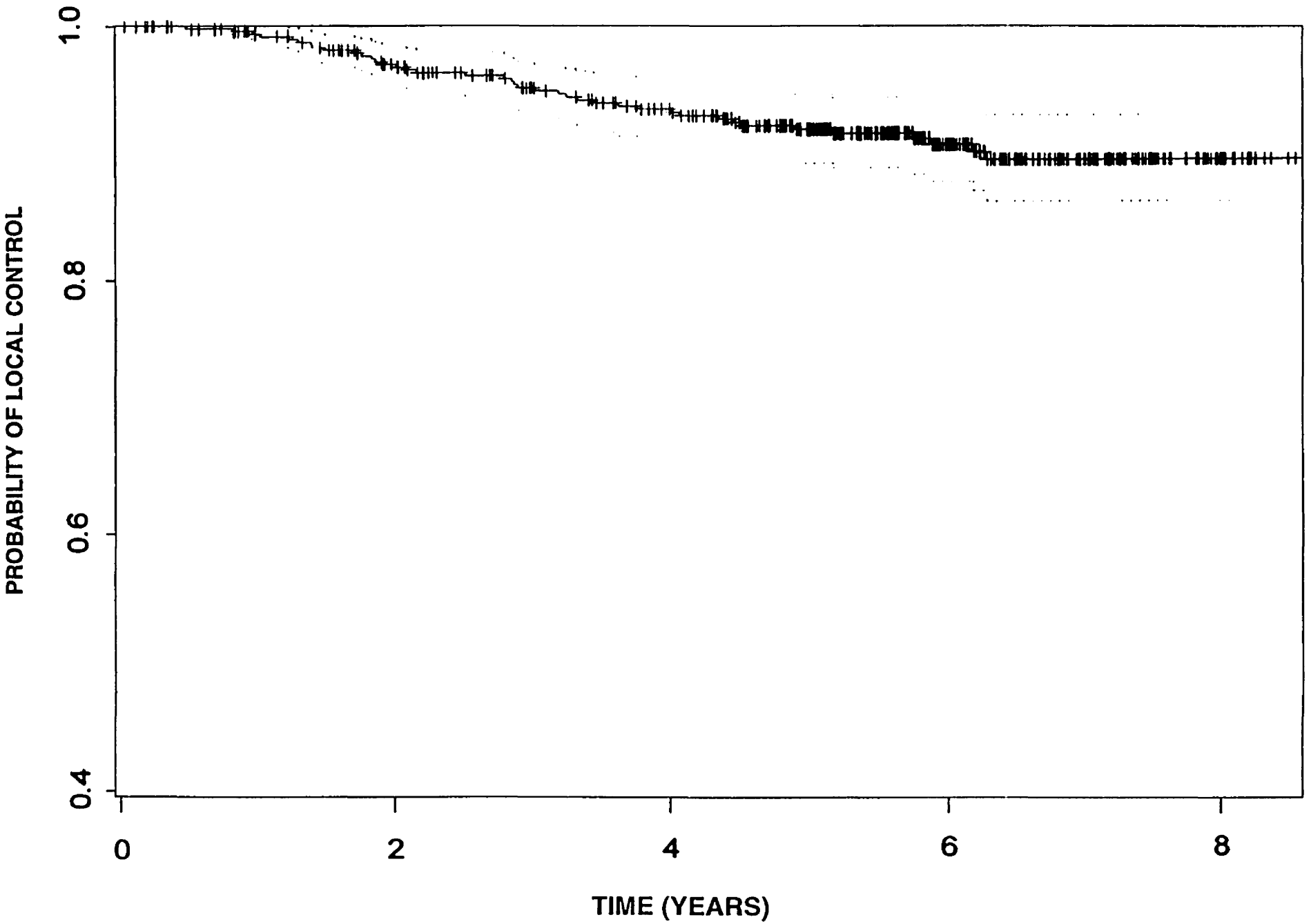


Figure 3

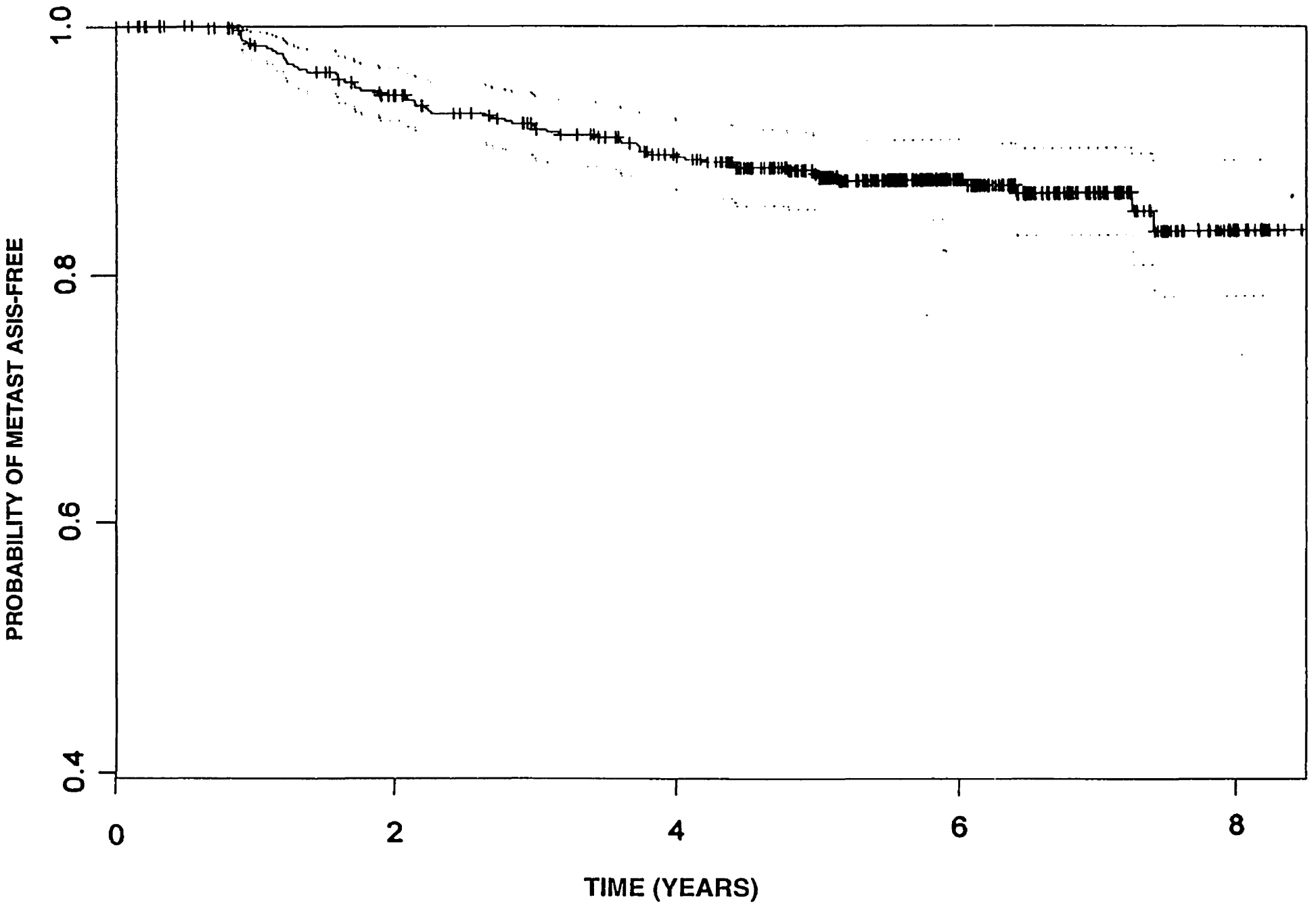


Figure 4

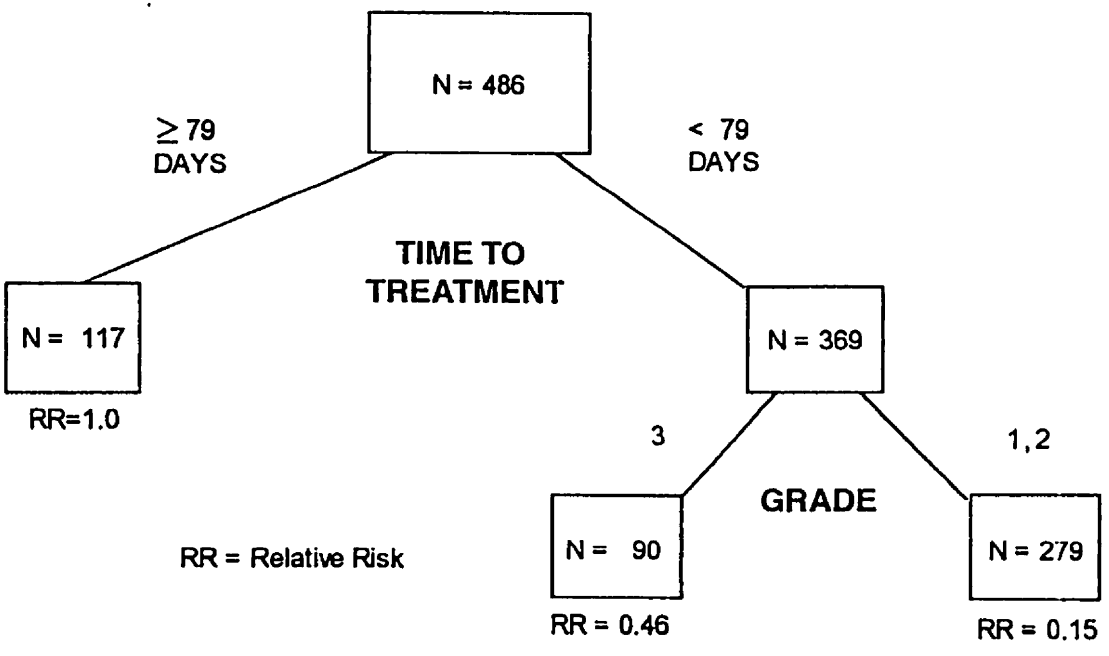
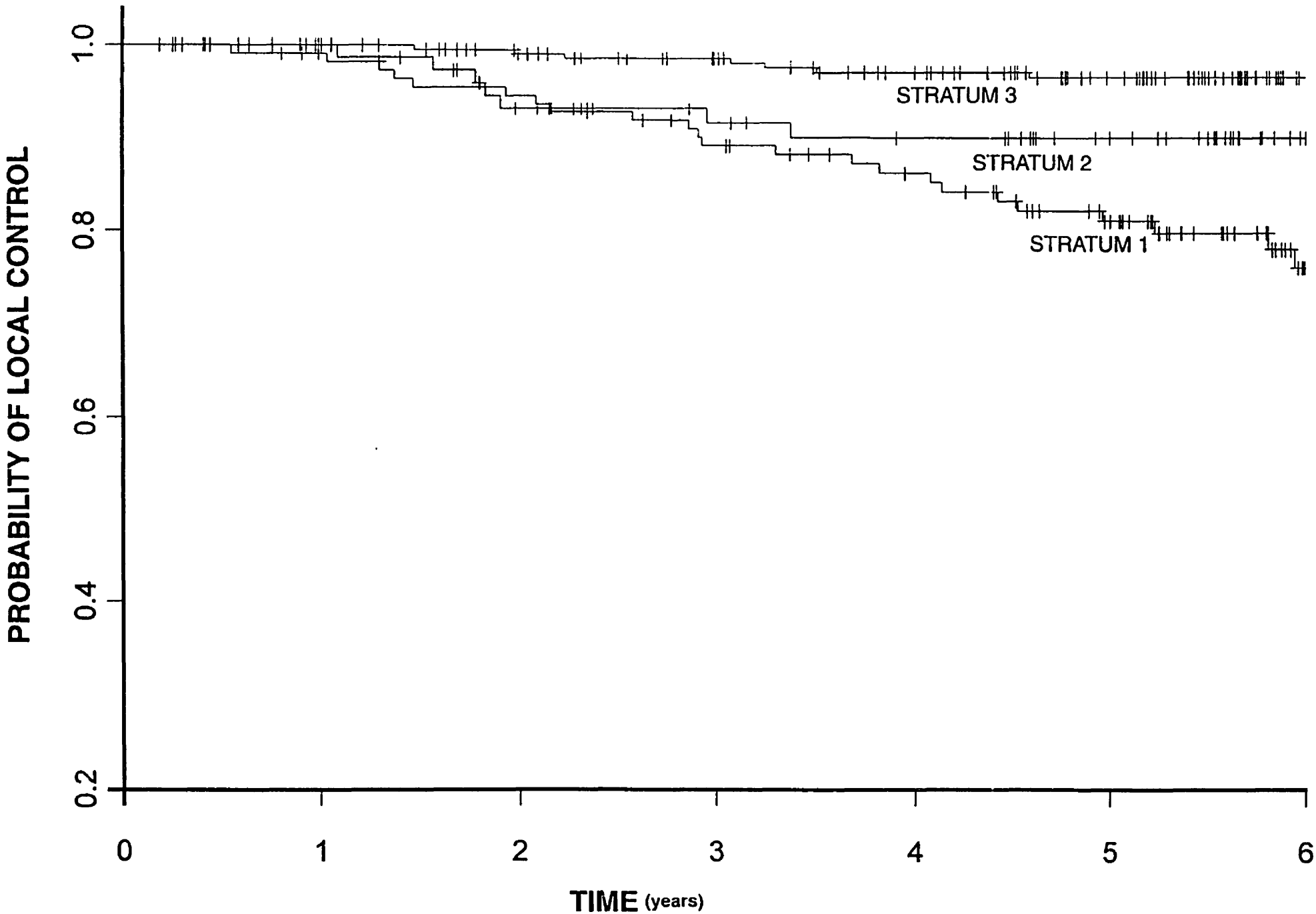

N = 486
≥ 79 DAYS
< 79 DAYS
TIME TO TREATMENT
N = 117
RR=1.0
N = 369
3
1,2
GRADE
RR = Relative Risk
N = 90
RR = 0.46
N = 279
RR = 0.15

Figure 5


PROBABILITY OF LOCAL CONTROL
1.0
0.8
0.6
0.4
0.2
STRATUM 3
STRATUM 2
STRATUM 1
0
1
2
3
4
5
6
TIME (years)

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Data Collection Form

TIME TO RADIATION THERAPY BREAST SURVEY II

Study ID#: _____

Hospital MRN#: __ __ __ __ __ __

DEMOGRAPHICS

Name: _____

Maiden Name: _____

Medicare Number: __ __ __ __ - __ __ __ __ - __ __ __ __

Date of Birth: __ __ / __ __ / __ __
d d m m y y

Age: __ __ __

Address: _____
_____
_____

Referral Centre: _____

Referral Physician: _____

CLINICAL PROFILE

Date of Surgical Procedure __ __ / __ __ / __ __
d d m m y y

Type:
- ☐ partial
- ☐ complete
- ☐ axillary node dissection

Histology:

Pathology: _____

Stage: I IIa IIb

Tumor size: _____

Grade: _____

Lymphatic invasion: Y N

Intraductal component: Y N

Margins: Pos Neg

Receptors: Pos Neg Not done

Lymph nodes:

- Number removed: _____
- Number positive: _____
- Unknown: _____

Irradiation:

Date of First Radiotherapy Evaluation: __ __ / __ __ / __ __ (d d m m y y)

Date of First Radiation Treatment: __ __ / __ __ / __ __ (d d m m y y)

Date of Last Radiation Treatment: __ __ / __ __ / __ __ (d d m m y y)

Dose: _____ Gray

Fractions Number: _____

Technique:

- ☐ Chest wall
- ☐ McGill
- ☐ Boost
- ☐ Other

Chemotherapy: Y N (Type) _____

Tamoxifene: Y N

Events

Date of First Event: __ __ / __ __ / __ __ (d d m m y y)

- ☐ local recurrence
- ☐ metastases (Specify) _____

Treatment Type:

- ☐ Radiotherapy
- ☐ Chemotherapy
- ☐ Surgery
- ☐ Hormones

Date of Last Visit: __ __ / __ __ / __ __ (d d m m y y)

Status:

- ☐ Dead
- ☐ Alive:
  - ☐ Complete Remission
  - ☐ Partial Remission
  - ☐ Progression
- ☐ Lost to follow-up