Waiting Time for Radiation Therapy in Non-Metastatic, Surgically-Treated Breast Cancer Patients in Quebec

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Abstract

The purpose of this study was to determine among surgically treated non-metastatic breast cancer patients in the province of Quebec the distribution of the time between surgery and post-operative radiation therapy (RT) as well as secular trends and other factors influencing waiting time. Using administrative records, I identified between 1992 and 1998 29,105 episodes of breast cancer and 17,704 of these contained an indication of receiving RT Hierarchical linear regression models were used to identify predictors of waiting time.

The number of cases of breast cancer increased by 5.5% per year while the number of those receiving RT increased by 9%. Median post-surgery waiting time was 75 days in 1992 and by 1998 it had increased by 63% (95% Confidence Interval (CI) 35% – 97%) among patients not requiring chemotherapy. In patients receiving chemotherapy, post-chemotherapy waiting time increased from 21 to 30 days (35% increase between 1998 and 1992 (95% CI -3% – 88%)). In addition to a significant variability of waiting time according to radiation therapy centre, predictors of shorter waiting times were earlier year of treatment, localised cancer stage, breast conserving surgery, early consultation with a radiation oncologist, being operated in a centre with a radiation therapy facility, living close to a radiation therapy facility, and living in a higher socio-economic area.

In conclusion, waiting time to start of radiation therapy after localised breast cancer increased substantially in Quebec from 1992 to 1998. Possible explanations include increased demand, insufficient resources and changes in the indications for breast conserving surgery and RT.
Résumé

Le but de cette étude était de déterminer, parmi les patientes atteintes de cancer du sein non métastatique traité chirurgicalement au Québec, la distribution, l'évolution temporelle et les facteurs affectant le temps d'attente pour la radiothérapie post-opératoire. Des bases de données administratives nous ont permis d'identifier 29 105 épisodes de cancer du sein, dont 17 704 parmi lesquels la radiothérapie était employée de 1992 à 1998. Un modèle hiérarchique de régression linéaire fut employé pour identifier les facteurs influant sur le temps d'attente.

Les nombres de cas de cancer du sein et de cancer du sein recevant de la radiothérapie se sont accrus respectivement de 5,5% et de 9% par an durant la période à l'étude. L'attente médiane qui était de 75 jours en 1992 s'est accrue en 1998 de 63% (intervalle de confiance (IC) à 95%, 35% – 97%) chez les patientes sans chimiothérapie. Chez celles recevant de la chimiothérapie, l'attente médiane post-chimiothérapie est passée de 21 à 30 jours, représentant une hausse ajustée de 35% (IC 95%, -3 – 88%). En plus d'une variabilité significative de l'attente entre les centres de radiothérapie, les facteurs prédictifs d'une attente plus courte étaient une année de traitement plus près de 1992, un cancer sans atteinte ganglionnaire, une chirurgie conservatrice, rencontrer précocement le radio oncologue, être opéré dans un centre où existe un service de radiothérapie, habiter près d'un tel centre et dans une région où le statut socio-économique moyen est plus élevé.

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This thesis is based on a study that was designed originally by Drs Mark Goldberg and Nancy Mayo that was used to investigate the distribution of time required in Quebec to obtain surgical treatments for breast cancer. They suggested to me to use this cohort of patients to investigate waiting times for radiation therapy treatments. Ms Susan Scott had done most of the data coding, cleaning and analysis for this previous project and has provided invaluable assistance. I was responsible for the literature review, the creation of the algorithms necessary to incorporate the information concerning radiation therapy and chemotherapy into the original data set, the coding and cleaning of the resulting data, performing the initial statistical modelling, and writing the thesis. Dr James Hanley, Ms Marie-France Valois, and Ms Scott provided help with the hierarchical linear modelling and its interpretation. Dr Mark Goldberg, as my supervisor, provided continual input during all the parts of the initial definition of the project, the statistical analyses, the interpretation of the models, the drafting of this thesis, and the presentation of the findings.

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1. Introduction

Over the last twenty years, the standard management for breast cancer has changed dramatically. Mammography has not always been in widespread use, with the consequence that breast tumours were often larger than those seen today,\textsuperscript{2,3} and surgery was more radical because there were no known effective complementary (i.e., adjuvant) treatments.

Gradually, findings from breast cancer screening programs showed a substantial survival advantage when the lesion is discovered early,\textsuperscript{4-8} an advantage that seems independent of lead-time bias.\textsuperscript{9} It has been found,\textsuperscript{9,10} although not completely consistently,\textsuperscript{11} that survival is poorer in breast cancer patients with prolonged time from onset of symptoms or suspicious screening to definite diagnosis. These results, added to the psychological distress caused by waiting,\textsuperscript{12} have prompted many governments, including Quebec, to institute breast cancer screening programs. In addition, guidelines have been published concerning the acceptable delays to complete all of the required diagnostic procedures.\textsuperscript{13}

Randomised controlled trials have shown the equivalence between extensive surgeries (radical and modified radical mastectomy) and the more conservative approach consisting of removal of the tumour with a small safe margin (breast conserving surgery) followed by radiation therapy.\textsuperscript{14-19} In addition, studies have shown the therapeutic value of systemic treatment (chemotherapy and hormonal therapy) in selected patients.\textsuperscript{20-22}

Despite the fact that radiation therapy has been used increasingly, there is still no consensus as to the optimal time for offering it. There is agreement that microscopic foci of tumour cells are responsible for local recurrences after conservative surgery, and that radiation therapy sterilises these foci. Theory and clinical experience also shows that larger doses of radiation are required to
sterilise a larger number of residual cancer cells.\textsuperscript{23,24} Thus, it is likely that early radiation therapy, before the residual cells multiply, will reduce the likelihood of local recurrences. On the other hand, the optimal time to radiation treatment also depends on waiting for the surgical scar to heal properly and, in patients who also need systemic treatments, on the toxicity of giving both radiation therapy and chemotherapy simultaneously.

The time required for healing after surgery is most often cited as being from two to four weeks.\textsuperscript{25,26} If the patient does not require chemotherapy, radiation therapy to the breast could be started approximately one month post-operatively. However, because resources are sparse, many patients in Quebec may wait many months before radiation therapy is started.\textsuperscript{27} The local recurrence rate after conservative surgery and radiation therapy is about 5\% and it increases to 20 to 50\% after conservative surgery without adjuvant radiation,\textsuperscript{19} which is equivalent to waiting indefinitely before giving radiation treatment. Coupled with reports that local control is possibly needed if survival is to be improved,\textsuperscript{28-34} it is reasonable to conclude that waiting time for radiation therapy should be minimised.

Defining the optimal sequence of treatments is complex when chemotherapy is also required because of the many possible scenarios: a) surgery followed by radiation therapy and then by chemotherapy; b) surgery followed by chemotherapy and then by radiation therapy; c) surgery followed by concomitant chemotherapy and radiation therapy; and d) other less used combinations such as pre-operative chemotherapy or radiation therapy. The main questions are as follows: is delaying chemotherapy more deleterious than delaying radiation therapy (trade-off between improved local tumour control and prevention of metastases)? Is the toxicity too high if both chemotherapy and radiation are given simultaneously? If chemotherapy is provided, can one wait to give
radiation therapy without compromising local tumour control? At present, we do not have definitive answers to any of these questions.

Combined with the ageing population\textsuperscript{35,36} and the increase in the incidence of breast cancer, the recent introduction of Quebec’s breast cancer screening program and advances in the treatment of breast cancer, especially the advent of breast conserving surgery followed by radiation therapy, have led to a potential increase in new indications for radiation therapy. Many physicians have expressed their concerns about the effect this may have on the availability of treatments in Canada.\textsuperscript{1,27,37,38} The latter report\textsuperscript{1} concerns waiting time from diagnosis to surgical breast cancer treatment in the population of Quebec from 1992 to 1998 and it showed that median waiting time has already been affected, especially after 1995, rising from approximately 30 days before 1996 to 42 days in 1998. Based on this report and the same cohort of patients, we decided to obtain information about radiation therapy treatments received to determine if there was also an effect on waiting time before radiation therapy.
2. Literature review

A search of the available literature was performed using MEDLINE, CANCERLIT and PUBMED electronic search engines for published articles about waiting time for treatments of breast cancer, including: delay from occurrence of breast cancer until symptoms, delay from the first symptoms until a diagnosis is made, delay from diagnosis until treatments are started and more specifically before the radiation therapy components of the treatment is started, and the possible effects of all of the previously stated components of delay on cancer control. The search strategy included the terms BREAST CANCER, WAIT, DELAY, SCREENING, RADIATION THERAPY, SURVIVAL, RECURRENCE, GUIDELINES. The search was restricted to English and French papers, human subjects, and full peer-reviewed reports. Pertinent references from the found original reports and review articles were also obtained. Some additional references were suggested by radiation oncologists, especially those concerning the role of radiation therapy in the modern sequence of treatments for breast cancer.

Delay from onset of cancer until diagnosis

The effects of the delay between non-symptomatic cancer occurrence and diagnosis have principally been investigated in various breast cancer screening trials\textsuperscript{2-8} which have led to the implementation of many country-wide breast cancer screening programs, including in the province of Quebec.

Briefly, the Canadian National Breast Screening Study-2\textsuperscript{2} did not show a significant reduction in mortality from breast cancer, but the tumours found were much smaller in the screened compared to the control group and were also more often \textit{in situ} (having the potential to become cancerous but not yet invasive).
The other screening trials, namely the Swedish two-counties trial,\(^3\) the Edinburgh trial,\(^4\) the UK trial,\(^5\) the Malmo trial,\(^6\) the HIP (Health Insurance Plan, US) trial\(^7\) and the Finnish trial\(^8\) all showed statistically significant reductions in the screened group of the risk of breast cancer death (between 21 and 36%).

**Delays from onset of cancer symptoms until diagnosis**

Reports concerning the effects of delay from symptoms until diagnosis were numerous, but 87 of them were reviewed in a report commissioned in 1999 by the United Kingdom’s National Health Service Cancer Research and Development Programme.\(^9\) Results from the pooled analysis showed that patients waiting more than three months from the onset of symptoms until the start of treatment had a 12% lower 5-year survival, which was both statistically and clinically significant. Longer waiting was also associated with higher stage disease at diagnosis. This was shown again recently in a population based study from a German province.\(^10\) We can assume that women waiting more will not survive as well because they will have more advanced disease, so the delay between symptoms and diagnosis should be kept as short as possible.

**Delays from cancer diagnosis until treatment**

My focus in analysing these reports was to assess the impact on survival or local recurrence from the time from surgery. The studies in this section are summarised in Table 2-1.

One of the first reports about this question in breast cancer patients came from the Institut Gustave-Roussy.\(^39\) The investigators retrospectively identified a group of 436 patients treated with breast conserving surgery and radiotherapy (none with chemotherapy). They found 24 local recurrences, translating in an actuarial rate of 7% at 5 years. Using a Cox regression approach, the only characteristics
associated with poorer tumour control were tumour grade, radiation dose to the breast and the tumour bed, and the time between biopsy and radiation treatment. For the latter, the hazard ratio of local cancer recurrence was 3.3 for radiation at or later than 7 weeks compared to less than 7 weeks after surgery ($p<0.01$).

Recht$^{40}$ retrospectively reviewed 295 patients with early stage breast cancer who were all treated with conservative surgery, standard chemotherapy for at least three months, and radiation therapy. There were 26 local recurrences. No differences in recurrence rates (around 5% at five years) was noted if the radiation was started between 0 to 4, 4 to 8, 8 to 12 or 12 to 16 weeks after surgery but the rate increased to 35% for patients starting after 16 weeks, even though all patients in that latter group were receiving an effective chemotherapy regimen during the whole duration of the waiting period from surgery until radiation therapy. The local control risk was statistically higher even though the number of patients at risk in the delayed radiotherapy group ($n=34$) was small. No deleterious effect was seen on overall survival by delaying radiation therapy, nor was there a benefit in giving the chemotherapy earlier, and chemotherapy did not seem able to prevent local failures. Limitations of this study were an extremely short follow-up (only one patient observed for 5 years in the delayed RT group), the small numbers of events, the retrospective design, and the variability of the treatment protocols used.

Buzdar and colleagues$^{41}$ reviewed 522 patients with localised breast cancer who were treated with surgery, chemotherapy and radiation therapy according to different treatment protocols used at their centre over the years 1974-1990. They did not observe any statistically significant difference in local tumour control when comparing patients treated with chemotherapy first or radiation first, and they concluded that delaying radiation is an acceptable choice to allow for rapid initiation of systemic treatments. However most patients (85%) were
treated with total mastectomy, in which case radiation is now known to be of limited value except in the minority of patients with large tumours or other adverse prognostic factors. Despite this, more than 16% of the mastectomy patients with chemotherapy first locally recurred at 10 years compared to 8%, the difference being non-significant mainly because of the small number of patients at risk.

Buchholz and colleagues \(^{42}\) performed a similar study on 105 patients accrued over 10 years, and all treated with surgery (breast conserving or mastectomy), chemotherapy, and radiation. They were divided in groups according to the time between surgery and radiation, “early” being from 0 to 6 months and “late” more than 6 months. Actuarial local tumour control at 8 years based on 10 events overall was 98% for the “early” group, compared with 76% if the radiation was delayed, and this remained significant after correcting for different baseline characteristics of subjects (p=0.011).

Nixon \(^{43}\) analysed retrospectively outcomes on 591 patients with early stage breast cancer who did not receive adjuvant chemotherapy and who were followed for five years. The patients were almost evenly divided in early (0-4 weeks) and late (5-8 weeks) post-operative radiation, patients waiting more than eight weeks were excluded. Baseline characteristics were similar in these two groups. No statistically significant differences were found in local recurrence rates. A number of limitations may make this study not applicable to Quebec: Nixon’s local recurrence rate was seven to 13%, which is high. The maximum waiting time was only eight weeks (less than the median delay in Quebec) and the status of the surgical margins was not assessed.

Slotman \(^{44}\) reported on 508 patients treated with breast conserving surgery and radiation, and some patients were also treated with chemotherapy. The delays between surgery and radiation therapy were not planned but occurred because
of equipment shortages, wound healing delays, or late referrals. No differences in treatment or patient factors were noted between the groups. Despite a low recurrence rate, factors significantly predicting local recurrence were T stage (AJCC tumour classification\textsuperscript{45}), status of surgical margins, and interval between surgery and radiotherapy. The local recurrence rate was 0% (0/42) in patients treated in less than 25 days, 2.0% (5/256) in those treated between 25-50 days, 5.4% (10/184) if between 50 and 75 days and 6.3% (2/32) if more than 75 days elapsed between surgery and radiation therapy. The waiting time before radiation therapy did not, however, affect survival or the rate of distant metastases.

Hartsell\textsuperscript{46} published another retrospective analysis of 84 patients who had lymph nodes positive breast cancer and who were treated with breast conserving surgery and chemotherapy. Radiation therapy was qualified as “early” if given before four months post-surgery. Overall survival was similar between groups, but local recurrence was significantly more frequent in the “delayed” group (14% vs. 2%, p=0.05).

Vujovic\textsuperscript{47} reported on 568 node-negative breast cancer patients treated with breast conserving surgery, radiation therapy, but not with chemotherapy. Local recurrence rates were calculated for patients receiving radiation therapy either before or three months post-surgery and were not significantly different (7.8% and 3.8% at five years respectively). The main difficulty in interpreting their results is that there was a significantly shorter follow-up time in the patients waiting longer for their radiation therapy, caused by a progressive increase in Ontario in the waiting lists for radiation therapy. Thus, most patients in the “delayed” radiation therapy group were treated in more recent years, and had also less time to recur, than patients in the “early” group. Also, there was a 4.8% rate of positive surgical margins (cancer at the surgical resection line) in the “early” group compared to 1.5% in the delayed group. Since positive surgical
resection margins is often cited as a strong predictor of local recurrence, this may be enough to offset a small difference in local recurrence rate but an adjusted analysis was not performed.

In British Columbia, Froud et al. reported on 1,962 patients treated with breast conserving surgery and radiation therapy without chemotherapy between 1989 and 1993. No differences in local breast cancer recurrence rates were found between intervals of 0 to 20 weeks from surgery to start of radiation therapy. However, as in the Ontario study cited above, there was a shorter follow-up time in the delayed radiation group because of an increasing waiting list for radiation therapy treatments. Another problem hindering generalisation to the Quebec population was that only 14% of patients had to wait more than 90 days compared to 37% in Quebec (see results below).

Because of the possibility of a harmful effect in delaying radiation therapy, Recht and colleagues conducted a randomised trial. Two hundred and forty-four patients with stage I and II breast cancer but with features warranting the use of chemotherapy were assigned randomly, after breast conserving surgery, to receive a 12 week course of chemotherapy given either before or after radiotherapy. Baseline characteristics (menopausal status, age, oestrogen receptors, surgical margins, number of nodes recovered at surgery) were distributed equally among the two groups. Median follow-up time was of 58 months. There was a lower overall survival (73 vs. 81%), higher distant metastasis rate (36 vs. 25%) but lower local recurrence rate (5 vs. 14%) in the group receiving radiotherapy early (thus delaying chemotherapy). None of these differences were statistically significant. Moreover, patients receiving radiation therapy first had to have their chemotherapy doses reduced more frequently due to side-effects. The low power of this study to detect small differences was unfortunate as no firm conclusions can be drawn from this potentially informative trial.
A systematic review was been published recently,\textsuperscript{50} including most of the retrospective series reported above, the randomised clinical trial, and some non-English and abstract-only literature in an attempt to reduce publication bias. Even though the quality of the available data is variable as seen before, randomised trials on waiting time are unlikely to be performed based on obvious ethical issues so the authors conducted a pooled analysis of the results using a random effects model using the adjusted recurrence rates from the publications to minimise the effects of differing baseline patient characteristics. By using the adjusted rates in their calculations and by including studies in which the main purpose was to study the optimal sequencing of chemotherapy and radiation therapy (in which patients who receive delayed radiation receive chemotherapy while waiting) the authors believe that if the pooled analysis is biased, it is likely biased towards minimising the detrimental effect of waiting rather than exaggerating it. No significant heterogeneity was found between the selected studies. The pooled odds ratio of local breast cancer recurrence comparing patients treated later than eight weeks to those receiving their post-operative radiation therapy within eight weeks was 1.62 (95\% confidence interval (CI) 1.21 - 2.03). The authors concluded that there is evidence that delay in initiating radiotherapy has an adverse effect on local control and recommend that those delays should be as short as reasonably achievable.

Considering the available data, the best estimate of the effect of delaying radiation therapy over eight weeks after surgery is to increase the risk of local recurrence by about 60\% compared to patients receiving radiotherapy within eight weeks. Nothing can be said about the effects of this increase in local cancer failure on overall survival, but overall cancer control requires local cancer control.
Delays observed for radiation therapy in breast cancer patients in other series

The final purpose of this literature review was to identify reports of lengthening delays before radiation therapy treatments to compare to the Quebec experience.

We already knew that waiting times for the surgical component of breast cancer treatment were increasing in Quebec because of the analysis performed previously.\(^1\) A first report from Ontario depicts a situation that is also deteriorating over time\(^3^8\). In 1991, the median time between the completion of surgery and initiation of post-operative radiation for breast cancer was of 57.8 days, which represents an increase of 102.7% compared to 1982 and was highly statistically significant. The same group then surveyed in 1994 major radiation centres in the United States and in Canada.\(^3^7\) Their study showed that for patients who are treated in the United-States the median waiting time before radiation therapy was forty days and was of 73 days in Canada. A separate report from a single centre in Quebec in 1992 showed a median waiting time of 68 days.\(^2^7\) Some literature from Europe suggests that waiting time are comparable to what is seen in the United States, with a Spanish report showing an overall maximal waiting time of only 60 days for all cancer types and centres in their country.\(^5^1\)

To summarise the above review, it seems important to diagnose breast cancer as early as possible since delaying its identification leads to a lower survival and providing a swift treatment seems to improve the rates of cancer control. Reports also demonstrate that waiting times before initiating radiation therapy treatments are longer in Canada and Quebec than in many other countries, but these reports are either single institution or survey based and do not provide a good idea of the temporal evolution of waiting times.
3. Objectives

The purpose of this study was to determine how waiting time for radiation treatment for breast cancer has changed in Quebec from 1992 to 1998. My primary hypothesis was that waiting times have increased because of an increasing demand for radiation therapy and a concomitant reduction in the availability of resources, and that this has translated on a population level into an increase in waiting for post-operative radiation therapy.

The specific objectives of the thesis are:

1. To estimate the number of women in Quebec with breast cancer during the period 1992 to 1998 who were treated surgically;
2. To determine secular trends in the treatments offered (type of surgery, proportion of patients receiving radiation and chemotherapy);
3. To evaluate the waiting time for radiation therapy among women who were surgically-operated, by type of adjuvant therapy; and
4. To identify factors associated with waiting time for radiation therapy.

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Abstract

**Background:** The purpose of this study was to determine among surgically treated non-metastatic breast cancer patients in the province of Quebec the distribution of the time between surgery and post-operative radiation therapy (RT) as well as secular trends and other factors influencing waiting time.

**Methods:** Records of physician fee-for-service claims and of hospitalisations were obtained for all Quebec women who underwent an invasive procedure for the diagnosis or treatment of breast cancer between 1992 and 1998. For non-metastatic breast cancer patients not receiving chemotherapy, waiting time was calculated as the number of days between the last surgical procedure and initiation of RT. For subjects receiving chemotherapy between the surgical procedure and the initiation of RT, waiting time was calculated as time between the last chemotherapy and the start of RT. Hierarchical linear regression models were used to identify predictors of waiting time.

**Results:** Over the seven year period 29,105 episodes of breast cancer were identified and 17,704 of these contained an indication of receiving RT. The number of women diagnosed with breast cancer increased by 5.5% per year, the proportion of patients treated by breast conserving surgery increased by 0.7% per year, and the proportion of patients treated with a breast conserving surgery and receiving RT increased by 1.8% per year, thus leading to a dramatic increase of 9% per year in the number of breast cancer patients requiring RT. Median waiting time was 75 days in 1992 and increased in 1998 by 63% (95% Confidence Interval (CI) 35% - 97%) in patients not requiring chemotherapy and in patients receiving systemic treatments, waiting time increased from 21 to 30 days, representing a 35% (95% CI -3% - 88%) increase from 1998 to 1992. There was considerable variation in median waiting times between radiation therapy centres. Other predictors of shorter waiting times were earlier year of treatment, localised cancer stage, breast conserving surgery, early implication of the radiation oncologist in the treatment process, being operated in a centre with a radiation therapy facility, living close to a radiation therapy facility and in a higher socio-economic area.

**Interpretation:** Possible explanations in the increased waiting time include increased demand, insufficient resources, and changes in the indications for breast conserving surgery and RT.
Introduction

During the last twenty years, management of breast cancer has changed dramatically. With mammography, breast tumours are now usually quite small and surgery is less radical because of effective adjuvant treatments. Randomised controlled trials have shown the equivalence between extensive surgery (radical and modified radical mastectomy) and a more conservative approach consisting of removal of the tumour with a small safe margin (breast conserving surgery) followed by radiation therapy.14-19

Despite the fact that radiation therapy has been used increasingly, there is still no consensus as to the optimal time for offering it. There is agreement that microscopic foci of tumour cells are responsible for local recurrences after conservative surgery, and that radiation therapy sterilises these foci. Theory and clinical experience also suggests that larger doses of radiation are required to sterilise a larger number of residual cancer cells.23,24 Thus, it is likely that early radiation therapy, before the residual cells multiply, will increase the chances of preventing a local recurrence. On the other hand, the optimal time to radiation treatment also depends on waiting for the surgical scar to heal properly and, in patients who also need systemic treatments, on the toxicity of giving both radiation therapy and chemotherapy simultaneously.

The demand for radiation therapy in treating breast cancer has increased over the past two decades as a result of the ageing population,35,36 the secular increase in the incidence of breast cancer, the recent introduction of breast cancer screening programs and the advances in the treatment of breast cancer (especially breast conserving therapy that also requires radiotherapy). Physicians have expressed their concerns about the effect that this increasing demand may have on the availability of radiation treatments in Canada.1,27,37,38 In Quebec, a recent report has shown that some women may have to wait many months
before radiation therapy is started.\textsuperscript{27} This may be important as it appears that the local recurrence rate after conservative surgery and radiation therapy is about 5\% but is 20 to 50\% after conservative surgery only,\textsuperscript{19} (equivalent to waiting indefinitely before giving radiation treatment). Coupled with reports that local control is possibly needed if survival is to be improved,\textsuperscript{28-34} waiting time for radiation therapy should probably be minimised. Because of the concerns about availability of services, we conducted the present study to estimate secular trends in waiting time for radiation therapy after breast cancer surgery and to identify factors that may influence waiting time.

\textbf{Subjects and Methods}

The study was population-based and included all women age 20 years and over who had an invasive procedure for the diagnosis or treatment of breast cancer in the province of Quebec between 1992 and 1998. This is the same study population as described in a paper on waiting times after surgical treatment.\textsuperscript{1} We used the database of physician fee-for-service claims maintained by the Régie de l'Assurance Maladie du Québec (RAMQ) to obtain data on diagnostic and surgical procedures related to the breast, including chemotherapy, radiotherapy, and visits to radio-oncologists. The validity and completeness of the RAMQ database have been verified and shown to be high\textsuperscript{52}. The hospital discharge file (referred to as MedEcho) was also used to capture additional details concerning the treatments received.

The following variables were provided: age of the patient in 1992 in 5-year categories; the Forward Sorting Area (i.e., the first three characters of the postal code); cancer stage, treating physician encrypted identifier, hospital encrypted identifier and coded markers for surgery type, radiation therapy, and chemotherapy. We used the Canadian census from 1996 to obtain for each Forward Sorting Area the median income, the proportion of households for which
high school was completed, and the distance of the patient’s residence to the nearest radiation therapy facility (in strata of 100 km).

The algorithms for extracting the diagnostic and surgical procedures have been published previously but are briefly reviewed here. It was usual for women to have many breast-related procedures over the study period. We considered consecutive procedures to the breast that were separated in time by five months or less as part of a single “episode of care”. The choice of five months was made because clinical follow-up is often routinely recommended at six-month intervals and we wanted to ensure that a routine six-month follow-up would not be considered as part of waiting time from initial diagnostic procedure to surgery. We did not impose any restrictions on the total duration of an episode except that there should not be any continuous period of five months or more of "inactivity". Any adjuvant treatments delivered later than one year after breast cancer surgery were considered not to be part of the episode. Time to visits and procedures related to chemotherapy and radiotherapy within an episode was thus counted from the date of surgery.

The period of time considered for this study was from 1992 to 1998 but prior (1989-1991) and subsequent (1999) data were used to avoid truncating episodes and joining treatment that spanned administrative time periods, respectively.

Treatment was considered to be for breast cancer if there was a record of hospitalisation or day-surgery on or around the time of surgery that was indicated on the RAMQ billing record with a diagnosis for breast cancer. Topography and morphology codes listed on the hospitalisation discharge database were used to estimate the stage of breast cancer as follows: localised (primary breast cancer with no reported lymph node involvement (ICD-9 174.0-174.9)); regional (primary breast cancer with lymph node involvement (code for primary breast cancer plus ICD-9 196.0-196.9)); disseminated (with metastases
beyond lymph nodes (primary breast cancer plus ICD-9 197.0-199.0));
carcinoma in situ (ICD-9 233.0); and breast neoplasms of uncertain behaviour
(ICD-9 238.3).

Only episodes including a breast surgery followed by adjuvant radiotherapy were
retained for further analysis. Episodes with a diagnosis of disseminated disease,
episodes of localised breast cancer occurring after an episode for metastatic
cancer, and those in which radiotherapy was begun prior to surgery were
excluded.

The typical sequence of events when preparing a radiation therapy treatment are
as follows: 1) the patient is seen by a radiation oncologist for an initial
consultation; 2) the treatments are planned (the treatment simulation); 3) calculations (dosimetry) are conducted to estimate the required radiation fields
arrangement, which must then be approved by the radiation oncologist; 4) the
treatments are begun and given on a daily basis for four to six consecutive
weeks and verified by a radiogram (referred to as the verification film) made
using the treatment X-ray or gamma beam usually at the first treatment; and 5) the patient is seen by the radiation oncologist on a regular basis during and after
treatments.

Although there are a variety of procedure codes used by the RAMQ, they can be
broadly classified into one of these five previously mentioned categories. Using
these codes, we developed an algorithm to identify the most probable date of
the initiation of radiation therapy (examples are shown in Figure 4-1).
Radiotherapy was deemed to have been provided when it was reported on at
least one billing record for verification (RAMQ code 8519). The date of initiation
of radiation therapy was assigned to the first verification code found in the
episode. When no verification code was found, we searched for a simulation or
dosimetry code (codes 8507, 8508, 8509, 8511, 8518, 8520, 8553) combined
with a post-treatment visit code (codes 9131, 9133, 9134, 9136, 9141, 9143, 9144, 9146, 9214, 9215) to capture the few patients in which no verification films were done (206 subjects, 1.16%). In those patients, the start date for radiation therapy was assumed to be the date of the last simulation or dosimetry billing code occurring before a post-treatment visit. There are no indications in these administrative databases of the total dose actually received, so we assumed that a patient in which radiation was started completed the full course of treatments. Some episodes contained only a simulation or dosimetry code but no other indications of treatment, and it was assumed that radiation therapy had not been given (1,121 occurrences; 6%). To determine if the radiation oncologist was implicated in the treatment decisions early in the process, we searched for any consultation code billed before the definitive surgery (codes 9160, 9165, 9168, 9170, 9176, 9212).

For patients who did not receive chemotherapy between their surgery and the initiation of radiation therapy, waiting time was calculated as the number of days that elapsed between the last definitive surgery for breast cancer found in an episode (accounting for possible multiple surgeries for a cancer) and the initiation of radiotherapy. For patients who received chemotherapy (code 0734) between the definitive surgery and the initiation of radiotherapy, the time before the end of the chemotherapy was considered as part of planned treatment and, thus, the waiting time was calculated as the time from the last post-operative chemotherapy code to the initiation of radiation therapy (Figure 4-2). Thus, because of these two definitions for waiting time, the patients with and without chemotherapy were analysed separately.
Statistical analyses

Secular trends in the number of cases of surgically-treated breast cancer, use of breast conserving surgery, use of chemotherapy or radiotherapy use were analysed using simple linear regression and logistic regression, respectively.

To evaluate factors associated with waiting time, linear regression models were used. We used the natural logarithm scale for waiting time because it was log-normally distributed. As waiting times could be expected to be more similar for patients treated in the same hospital, we made use of hierarchical linear models. We did not treat each radiation oncologist as a clustering variable because in most centres the waiting list is not managed by individual doctors but at an institutional level. The rationale for using these more complicated models was to account for clustering within treatment centres that would lead to violations of independence required by standard regression methods, biased estimates of effect, and underestimated variances.

We used two-level mixed models to separate the effects of the radiation therapy centre from the effects of individual-level variables (e.g., tumour stage). The hierarchical approach allowed us to model waiting time in terms of patient-level variables but allowing for a different median values for different radiation therapy centres. The “random” component of a hierarchical model refers to the variability explained by the radiation therapy centres and the “fixed” component refers to the variability explained by individual-level variables.

By using a “random intercept”, we allowed each radiation therapy centre to have its own median value for waiting time and then the effect of any individual-level variable was analysed according to that centre-specific median. Using “random slopes”, we also allowed each individual-level variable to have a different effect depending on the radiation therapy centre in which the patient was treated. After
determining that a significant amount of variation in waiting time was explained by the treatment centre, we identified centre-specific variables that could account for this. Patient-specific attributes (fixed effects) were explored using regular multivariable linear regression and those with regression coefficients having a p-value lower than 0.10 were included in the hierarchical regression models.

Exponentiating the parameter estimates represents the adjusted relative change from the mean of the log waiting time, but since waiting times had a log normal distribution, this can be closely approximated by the median. All statistical tests were two-sided and the reported confidence intervals (CI) are at the 95% level.

**Results**

**Demographic characteristics**

Between 1992 and 1998, there were 30,479 episodes of surgically-treated breast cancers among 28,865 patients. Of those, 1,350 were metastatic and 24 were localised but occurred after a metastatic episode and these were excluded, thus leaving 29,105 cancer episodes.

Table 4-1 shows that the distribution of the stage of breast cancer was fairly stable during the study period (an average of 67% of cases classified as localised, 26% as regional, 7% as unspecified), although there was a secular increase in the number of unspecified cases. The age distribution was stable during the study period with roughly fifty percent of patients between 45 and 69 years old.

Table 4-2 shows the secular changes in the number of cases of surgically-treated breast by type of surgery, stage of disease, and adjuvant treatment. There was a
statistically significant average increase of 240 cases per year during the study period (5.5% per year, 95% CI 3.7 - 7.4%). The proportion of patients treated with breast conserving surgery rose by 0.7% per year (95% CI: 0.3 - 1.1%).

One of the key features of Table 4-2 is the sharp increase in the numbers of patients receiving radiation therapy (9% per annum; 95% CI: 5.7 - 12.4%), faster than the increase in the total number of cases of cancer. As well, for patients treated with breast conserving surgery, the proportion receiving radiation therapy increased from 65% to 77% over the same period (annual increase of 1.8%; 95% CI: 1.0 - 2.6%). On the other hand, the use of chemotherapy (~26% of patients) and radiation therapy for patients treated with mastectomy (average 22%) was stable.

**Waiting time for radiation therapy**

Post-operative radiation therapy was provided in 17,704 of 29,105 breast cancer episodes (60.8%). We grouped patients according to whether they received chemotherapy after the surgery and before radiation (4,827 patients) or not (12,877 patients).
Figure 4-3 shows the median waiting time by year of treatment for the group without chemotherapy (from surgery until radiation therapy) and for the group with chemotherapy (from the last post-operative chemotherapy cycle until radiation therapy). For the group without chemotherapy, the median waiting time in 1992 was 75 days and it increased by 21% by 1998; for the group without post-surgery chemotherapy, the median waiting time was 21 days and it increased by 33% by 1998.

Table 4-4 and Table 4-5 show the predictors of waiting time, expressed as the percent change from the median waiting time, for the non-chemotherapy and the chemotherapy group, respectively. For the hierarchical models, the fixed-effect estimates are provided (column two) and the estimated between-centre variation in the fixed effects is presented in the last column. Except for a few findings, the results using ordinary and hierarchical models were similar although variances are underestimated in the in the non-hierarchical models.

In the non-chemotherapy group, waiting times increased on average by 63% between 1992 and 1998. The hierarchical modelling demonstrated a more dramatic increase in waiting times than the unadjusted calculations mainly because of the opening of radiation centres (with shorter waiting time) in the latter years, artificially reducing the overall median waiting time. Indeed, the third column shows that there was considerable variation by radiation centre (the radiation centre in which a patient was treated explaining 30% of the variability). For example, the 95% CI between centres (random effects) varied from -11% to +199% from the average 63% increase in 1998 as compared to 1992. Other individual-level factors that also predicted waiting time were regional cancer stage (9% increase in waiting time), having had a mastectomy versus breast conserving surgery (25% increase), living further than 100 km from a radiation therapy centre (10%), seeing a radiation oncologist before being operated (-30%), being operated in a centre where there is a radiotherapy service (-13%),
and coming from an area in which average education is higher (-3%). The only
centre-specific (second level) variable that contributed to the model was the
centre being in a high income area (-2%). The individual-level variables in the
model only explained a small amount (15%) of the variation in the distribution of
waiting times (Figure 4-4).

For the chemotherapy group, the hierarchical modelling is included mainly for
completeness but the radiation therapy centre where a given patient was treated
explained only 2% of the variation between waiting times (Figure 4-4). The
effect of individual-level variables that predicted waiting time in this group was
similar in direction to what was found in the no-chemotherapy group. The
variables were regional cancer stage (35% increase in waiting time), having had
a mastectomy versus breast conserving surgery (34% increase), and being
operated in a centre where there is a radiotherapy service (-21%). A trend
towards longer waiting time was found in the latter years (35% longer in 1998
than in 1992). The parameters for the models in the chemotherapy group are
less stable because the cohort was smaller.

**Discussion**

The main findings from this study are that waiting times for receiving radiation
therapy after surgery for breast cancer increased in all patients, regardless as to
whether they received post-operative chemotherapy or not. Important
predictors of longer waiting times for patients were having a regional cancer
spread and having had a more extensive surgery, whereas a strong predictor of
a shorter waiting time was being operated in a centre where there is a radiation
therapy facility. In the larger group of patients not receiving post-operative
chemotherapy, we found that waiting times were longer for patients living far
from radiation therapy facilities and shorter for patients in which a radiation
oncologist was implicated early in the treatment process. Living in a higher socio-economic area was also associated with a slightly shorter waiting time.

Most of the variation in waiting times cannot be explained by the available data. This result is not surprising given that this study is based on administrative databases that contain very little data on personal characteristics, medical histories, and limited contextual variables on geographical areas. Given the current health care system’s status, it is unlikely that waiting times have improved dramatically since 1998. The increase in the group receiving chemotherapy is rather disturbing considering even if there is a planned delay of three to six months, it was not possible to maintain a stable waiting time during the study period. For patients not receiving chemotherapy between surgery and the start of radiation therapy, the unadjusted proportion of patients having to wait more than eight weeks before radiation therapy increased from 70% in 1992 to 82% in 1998 (Figure 4-5). If a twelve week cut-off is chosen instead, the proportion increased from 36% in 1992 to 57% in 1998.

The effect of socio-economic status on waiting time is surprising considering the universal health insurance coverage in the province of Quebec. It may reflect having an ability to insist or otherwise influence more timely treatment.

The significant effect of distance from the nearest radiation therapy centre is troubling and emphasises the importance of swift communication between the treating surgeon and the radiation oncologist.

A favourable effect on waiting time was found for patients operated in a centre with a radiation therapy facility on-site. These centres are mainly large tertiary centres, as radiation therapy is not offered outside of a hospital setting. Some explanations for this effect include improved communication between specialists,
faster access to diagnostic tests, and higher volumes of patients treated by these surgeons.

The other factors adversely affecting waiting time were having had a mastectomy and having regional disease spread. The longer waiting time could have been due to longer healing time after a more important surgery, or to more thorough investigation and treatment for a more severe disease.

Some radiation therapy centres performed better than others. This is not explainable using the available data because each hospital designation code was encrypted for confidentiality reasons. Thus it is difficult to explore possible causes for poorer performance such as total radiation therapy workload, staff shortage, case mix or other reasons. However, it is likely that some of the radiation centres were newly created and thus may not have had the same backlog as the older ones.

A strength of this study is that it is population-based and that the data are robust: physicians are paid on the basis of services rendered, and completeness and accuracy of reporting have monetary incentives attached. Because of the universality of Medicare, very few procedures would have been performed at private clinics and, thus, coverage of the data is close to 100 percent. The waiting times for radiation therapy reflected in this study are thus a precise depiction of the situation in Quebec.

A limitation of this study is that these results cannot be used to distinguish system delays from patient delays, as our data sources only contain records for procedures performed by physicians. Nevertheless, in an oncology setting, the delay for which the patient is responsible is often only the time from the appearance of symptoms until the first contact with a health care professional,
the following diagnostic and therapeutic procedures being scheduled for the patient from then onwards.

There are no data to suggest what should be an optimal waiting time. As treatment decisions involve major life altering choices for women, an "appropriate" amount of time is required to choose the best treatment approach,\textsuperscript{54} and this may vary considerably between women. On the other hand, there may be considerable anxiety faced by women and their families because of delays. What is of more concern is if long waits also affect recurrence and survival, as is suggested by theory and experience in other cancer sites.\textsuperscript{55-58}

There is only one randomised clinical trial\textsuperscript{49} and few retrospective studies investigating the effects of delays on breast cancer control,\textsuperscript{39-44,46-49} summarised in Table 2-1. In this trial, 244 patients with early breast cancer were assigned randomly, after breast conserving surgery, to receive a 12 weeks course of chemotherapy given either before or after breast radiotherapy. The characteristics of the groups were similar. Median follow-up was of 58 months. There was a lower overall survival (73 vs. 81%), higher distant metastasis rate (36 vs. 25%) but lower local recurrence rate (5 vs. 14%) in the group receiving radiotherapy early (thus delaying chemotherapy). These observations have lead to the practice of prioritising chemotherapy in patients who require it over radiation therapy.

In the other series from Table 2-1, either the low number of patients, the few events analysed, or the short follow-up reduced considerably the power to detect changes in cancer recurrences and death. One study showing no detrimental effect of delaying radiation therapy was conducted among patients mostly treated with a mastectomy, for which radiation therapy is rarely used.\textsuperscript{41} In some reports, the baseline characteristics of subjects between the study groups differed markedly and this could have led to biases in estimates of local
recurrence rates.\textsuperscript{42,47,48} In other papers, waiting times were extremely short so that it would have been surprising to see any differences, and their results may not be applicable to our population in which waiting times are much longer.\textsuperscript{43,47,48}

A pooled analysis of these and other studies was conducted\textsuperscript{50} for local breast cancer recurrence rates comparing patients treated later than eight weeks to those receiving their post-operative radiation therapy within eight weeks. The pooled odds ratio of local breast cancer recurrence comparing patients treated later than eight weeks to those receiving their post-operative radiation therapy within eight weeks was 1.62 (95\% confidence interval (CI) 1.21 - 2.03). Despite the fact that the quality of the data available for pooling was not optimal as discussed above, there was no significant heterogeneity in the results.

A study directly studying the effects of increasing delays before radiation therapy is unjustifiable based on the presented body of evidence and would only serve the purpose of knowing the efficacy of radiation therapy given in a context of scarce resources, an uncommon situation in most countries at the present time. Because it is unethical to withhold treatment, only observational studies can shed light on the effects delays for treatment, although a randomised trial evaluating the optimal sequencing of multimodality (i.e., surgery, chemotherapy, hormonal therapy and radiotherapy) breast cancer treatment could be conducted, but again the pure effect of delaying radiation therapy in patients for which chemotherapy or hormonal therapy are not indicated could only be inferred.

The best available estimate of the effect of delaying radiation therapy over eight weeks after surgery is to increase the risk of local recurrence by 60\% compared to patients receiving radiotherapy within eight weeks. The existing data do not show an effect of local cancer recurrence rates on survival. The usually slow tumour kinetics of breast cancer leading to an under-detection of late recurrences in studies with short observation periods and the option to perform a
mastectomy in patients locally recurring after a breast conserving surgery may be possible explanations for this lack of obvious relationship between local recurrences and cancer death. Nevertheless, even local recurrences can be psychologically devastating and local cancer control remains a *sine qua non* component of cancer cure.

**Conclusions**

Using administrative databases, we found a substantial increase in the time patients have to wait to receive post-operative radiation therapy for breast cancer in the province of Quebec, whether they receive chemotherapy or not. This may be explained by a sharp and unrelenting rise in the number of patients presenting with localised breast cancer and by changing trends in the treatments algorithms of that disease over the study period. It was not possible to determine if the increasing delays in the initiation of radiation therapy have already translated in more breast cancer recurrences in our study population but we believe that it should be a priority of the public health system to reduce waiting times immediately.
5. Discussion, summary, and conclusions

Waiting to receive necessary treatments for breast cancer was a significant problem experienced by the majority of women in the province of Quebec between 1992 and 1998. Even though additional radiation therapy centres were opened after 1992, the situation continued to deteriorate even faster in the latter years of this study. Temporary measures were, however, implemented after 1998 in an effort to improve the timeliness of radiation therapy treatments: accelerated formation programs for radiation technologists, funds dedicated to the acquisition of new radiation therapy units, extended working hours in radiation therapy departments, delivery of temporary work permits to non-Canadian physicians, and arrangements with out-of-province radiation therapy facilities.

Nevertheless, it is unclear whether these measures are effective because of the increased workload in health care providers or the increased costs for out-of-province treatments. The situation is thus far from corrected, and there is no reason to believe that the increase in the number of breast cancer cases demonstrated in this study will plateau in the next few years. Let us assume that the incidence of all non-breast cancers remain stable, there is an average of 240 more patients with breast cancer requiring radiation therapy each year (from our study), each patient requires from 20 to 25 radiation sessions, and each radiation therapy unit treats on average 30 to 40 patients per day, 250 days per year. Under these assumptions, we would need between 0.5 and 0.8 new radiation therapy units per year, with the health care workers required to operate them, just to maintain the same waiting times.

The main argument against increasing the resources dedicated to the timely treatment of breast cancer is the difficulty to prove that delaying treatments have an adverse effect on cancer outcome. Treatment delay is not a widespread
phenomenon in most developed countries. The fact that our health care system has difficulty providing timely treatments may be secondary to its greatest virtue, universal coverage. As a consequence of the fact that only few countries face our waiting problems, the literature concerning the effects of treatment delays is sparse and no important medical association has provided a useful definition of what should be considered the maximal time acceptable before treatments are offered.

Despite this, as discussed above, data does exist and the literature has shown that longer waiting times before treatment are associated with an increase in breast cancer recurrences. This fact is supported by theory and by experience with other cancer types.

Efforts have been made to minimise the resources needed to treat patients, for example by experimenting with shorter but still effective radiation schedules, new radiation delivery systems are being evaluated to allow to treat selected patients in one week only, but time and human resources are needed to perform these evaluations. Considering the rapid rise in the number of patients requiring treatments each year in the province of Quebec, a more effective utilisation of the available resources will have to be developed, swifter communication between all the members of the treating team should be encouraged, but it also appears clear that this alone will not be sufficient.

With 38 radiation therapy units available province-wide in 1998, the three that opened during the study period would have been barely sufficient to maintain stable waiting times if only the number of breast cancer cases was increasing. Reality is very different from this assumption. Even if the age-standardised incidence of most cancer types has decreased in Canada in the last 10 years, the total number of cancer cases has doubled in the last 30 years alone, reflecting the increase and the ageing of the population.
More resources will ultimately be needed if we are to prevent waiting time for radiation therapy treatments to increase further: more doctors to evaluate the patients and to develop less time-consuming techniques, medical physicists to maintain the radiation units in good working order, to validate new units and new techniques, more radiation technologists to make better use of the equipment already available and almost certainly more radiation therapy units once those in place are functioning extended hours on a permanent basis when enough technologists will be available.
6. References


13. The palpable breast lump: information and recommendations to assist
decision-making when a breast lump is detected. The Steering Committee
on Clinical Practice Guidelines for the Care and Treatment of Breast
Cancer. Canadian Association of Radiation Oncologists. CMAJ 1998; 158
Suppl 3:S3-S8.
al. Breast conservation is the treatment of choice in small breast cancer:
15. Sarrazin, D., Le, M. G., Arriagada, R., Contesso, G., Fontaine, F.,
Spielmann, M. et al. Ten-year results of a randomized trial comparing a
conservative treatment to mastectomy in early breast cancer. Radiother
Oncol 1989; 14(3): 177-84.
16. van Dongen, J. A., Bartelink, H., Fentiman, I. S., Lerut, T., Mignolet, F.,
Olsthuys, G. et al. Randomized clinical trial to assess the value of breast-
conserving therapy in stage I and II breast cancer, EORTC 10801 trial. J
K., Andersen, K. W. et al. Danish randomized trial comparing breast
conservation therapy with mastectomy: six years of life-table analysis.
Danish Breast Cancer Cooperative Group. J Nati Cancer Inst Monogr
18. Jacobson, J. A., Danforth, D. N., Cowan, K. H., d'Angelo, T., Steinberg, S.
M., Pierce, L. et al. Ten-year results of a comparison of conservation with
mastectomy in the treatment of stage I and II breast cancer. N Engl J
N. Twenty-five-year follow-up of a randomized trial comparing radical
mastectomy, total mastectomy, and total mastectomy followed by
20. Polychemotherapy for early breast cancer: an overview of the randomised
352(9132):930-42.
21. Tamoxifen for early breast cancer: an overview of the randomised
22. Goldhirsch, A., Glick, J. H., Gelber, R. D., Senn, H. J. Meeting highlights:
International Consensus Panel on the Treatment of Primary Breast Cancer.
24. DeVita, Vincent T., Hellman, Samuel, Rosenberg, Steven A. Cancer -
1998.


-35-


-36-


Table 2-1: Studies describing the effects of delaying post-operative radiotherapy

<table>
<thead>
<tr>
<th>Series</th>
<th>Study design and comments</th>
<th>Local recurrence</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarke et al, 1985&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Retrospective, 436 patients with T1 or T2 tumours, 24 recurrences overall. Time between biopsy and RT ≥ 7 weeks vs. &lt; 7 weeks (reference), Cox regression analysis. Mean waiting time of 4.4 weeks, only 12% waited more than 7 weeks</td>
<td>7% at 5 years overall, univariate RR 3.3 (p=0.01) favouring early radiation</td>
<td>no significant difference</td>
</tr>
<tr>
<td>Recht et al, 1991&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Retrospective, 295 patients, all treated with BCS, all received chemotherapy either before or after RT. Time between last surgery and RT &gt; 16 vs. ≤ 16 weeks. Only 9% of patients waited &gt; 16 weeks, only 9 patients at risk at 5 years</td>
<td>35% vs. 5% at 5 years favouring early radiation, log rank p = 0.0001</td>
<td>no significant difference</td>
</tr>
<tr>
<td>Buzdar et al, 1993&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Retrospective, 522 patients, all with CT. 85% mastectomies. Compared group CT first (minimum wait before RT of 20 weeks) vs. group RT first</td>
<td>4% in both groups at 5 years, no significant difference</td>
<td>no significant difference</td>
</tr>
<tr>
<td>Buchholz et al, 1993&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Retrospective, only 105 patients over 10 years, all had CT, any surgery. Wide variation of patient and treatment characteristics between groups. Stratification less vs. more than 6 months between surgery and RT</td>
<td>at 8 years, 2 vs. 24% favouring early radiation, p = 0.004</td>
<td>at 8 years, 80 vs. 52% favouring early RT, p = 0.016</td>
</tr>
<tr>
<td>Nixon et al, 1994&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Retrospective, 591 patients without CT, baseline characteristics similar, no patients waited more than 8 weeks for RT. Groups stratified in early post-op RT (0-4 weeks) vs. late (4-8 weeks)</td>
<td>13% vs. 7% local recurrence only at 5 years favouring early radiation, n.s.</td>
<td>not stated</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Patients</td>
<td>Follow-up Period</td>
</tr>
<tr>
<td>------------------</td>
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<tr>
<td>Slotman et al, 1994&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Retrospective, 508 patients with BCS, some with CT. Baseline characteristics similar between groups. Stratification more vs. less than 50 days between surgery and RT</td>
<td>crude risk over study period 1.7 vs. 5.6% favouring early RT, remains significant on multivariate analysis</td>
<td>no significant difference</td>
</tr>
<tr>
<td>Hartsell et al, 1995&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Retrospective, 84 patients with BCS and CT, stratification more vs. less than 120 days</td>
<td>14% vs. 2% actuarial at 5 years favouring early RT, ( p = 0.05 )</td>
<td>not stated</td>
</tr>
<tr>
<td>Recht et al, 1996&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Prospective, 244 patients with BCS randomised to RT before CT or CT before RT, CT lasted 12 weeks.</td>
<td>5 vs. 14% at 5 years favouring RT first, borderline significance</td>
<td>73 vs. 81% at 5 years favouring CT first, borderline significance</td>
</tr>
<tr>
<td>Vujovic et al, 1998&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Retrospective, 568 patients with BCS and no CT stratified less vs. more than 12 weeks between surgery and RT. Very few patients waited more than 16 weeks (7%). Some important baseline characteristics unbalanced (see text)</td>
<td>7.8% (early RT group) vs. 3.8% (late RT group) n.s.</td>
<td>not stated</td>
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<tr>
<td>Froud et al, 2000&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Retrospective, population based, 1,962 patients with BCS and no CT. Stratification 0-5 vs. 6-8 vs. 9-12 vs. more than 13 weeks between surgery and RT. Follow-up significantly shorter in late RT groups. Few patients waited more than 13 week (14%)</td>
<td>3.3 vs. 2.2 vs. 2.8 vs. 2.4%, n.s.</td>
<td>not stated</td>
</tr>
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</table>

n.s.: not significant, CT: chemotherapy, RT: radiotherapy, BCS: breast conserving surgery
Table 4-1: Characteristics of the 29105 non-metastatic breast cancer episodes among the 28,865 patients surgically-treated in Quebec between 1992 and 1998

<table>
<thead>
<tr>
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<td>20-34</td>
<td>1488 (5.1)</td>
<td>2.6</td>
<td>3.6</td>
<td>3.9</td>
<td>4.8</td>
<td>5.9</td>
<td>6.2</td>
<td>7.5</td>
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<td>35-49</td>
<td>8968 (30.9)</td>
<td>25.4</td>
<td>28.4</td>
<td>28.9</td>
<td>30.5</td>
<td>31.6</td>
<td>34.1</td>
<td>34.6</td>
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<td>50-64</td>
<td>10092 (34.7)</td>
<td>33.5</td>
<td>33.7</td>
<td>34.6</td>
<td>34.8</td>
<td>35.1</td>
<td>34.8</td>
<td>36.0</td>
</tr>
<tr>
<td>65-79</td>
<td>7364 (25.3)</td>
<td>31.3</td>
<td>28.3</td>
<td>27.6</td>
<td>25.7</td>
<td>24.5</td>
<td>22.5</td>
<td>20.3</td>
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<tr>
<td>≥ 80</td>
<td>1160 (4.0)</td>
<td>7.3</td>
<td>6.1</td>
<td>4.9</td>
<td>4.2</td>
<td>2.9</td>
<td>2.4</td>
<td>1.6</td>
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<tr>
<td>Cancer stage</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Benign / In situ</td>
<td>199 (0.7)</td>
<td>0.6</td>
<td>0.8</td>
<td>0.9</td>
<td>0.7</td>
<td>0.6</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Localised</td>
<td>19336 (66.51)</td>
<td>66.2</td>
<td>67.0</td>
<td>66.8</td>
<td>65.4</td>
<td>66.6</td>
<td>66.5</td>
<td>67.0</td>
</tr>
<tr>
<td>Regional</td>
<td>7431 (25.6)</td>
<td>28.4</td>
<td>26.8</td>
<td>26.7</td>
<td>26.4</td>
<td>24.8</td>
<td>24.1</td>
<td>23.1</td>
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<tr>
<td>Unspecified</td>
<td>2106 (7.2)</td>
<td>4.8</td>
<td>5.3</td>
<td>5.7</td>
<td>7.5</td>
<td>8.1</td>
<td>8.8</td>
<td>9.1</td>
</tr>
<tr>
<td>Surgery in a centre with a radiation therapy service</td>
<td>8420 (29.0)</td>
<td>29.9</td>
<td>29.5</td>
<td>28.2</td>
<td>28.3</td>
<td>29.8</td>
<td>29.0</td>
<td>29.1</td>
</tr>
<tr>
<td>Highest quartile for median income</td>
<td>5846 (24.8)</td>
<td>22.9</td>
<td>24.2</td>
<td>24.9</td>
<td>24.2</td>
<td>25.6</td>
<td>26.0</td>
<td>28.3</td>
</tr>
</tbody>
</table>

Residential distance from a radiation therapy centre

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0-100 km</td>
<td>25960 (89.4)</td>
<td>88.5</td>
<td>89.8</td>
<td>89.8</td>
<td>88.8</td>
<td>89.0</td>
<td>89.6</td>
<td>89.9</td>
</tr>
<tr>
<td>101-400 km</td>
<td>2933 (10.1)</td>
<td>10.9</td>
<td>9.8</td>
<td>9.6</td>
<td>10.6</td>
<td>10.4</td>
<td>10.0</td>
<td>9.7</td>
</tr>
<tr>
<td>401 km or more</td>
<td>158 (0.5)</td>
<td>0.5</td>
<td>0.4</td>
<td>0.7</td>
<td>0.7</td>
<td>0.6</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Table 4-2: Distribution of the number of cases by type of treatment and calendar year

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of cases</td>
<td>3532</td>
<td>3675</td>
<td>3904</td>
<td>4062</td>
<td>4231</td>
<td>4503</td>
<td>5165</td>
<td>5.5% (3.7 to 7.4)</td>
</tr>
<tr>
<td>Proportion with BCS†</td>
<td>78%</td>
<td>78%</td>
<td>78%</td>
<td>80%</td>
<td>81%</td>
<td>80%</td>
<td>82%</td>
<td>0.7% (0.3 to 1.1)</td>
</tr>
<tr>
<td>Number receiving RT†, any surgery</td>
<td>1966</td>
<td>2125</td>
<td>2306</td>
<td>2393</td>
<td>2592</td>
<td>2886</td>
<td>3398</td>
<td>9.0% (5.7 to 12.4)</td>
</tr>
<tr>
<td>Proportion receiving RT, any surgery</td>
<td>56%</td>
<td>58%</td>
<td>59%</td>
<td>59%</td>
<td>61%</td>
<td>64%</td>
<td>68%</td>
<td>1.8% (1.2 to 2.4)</td>
</tr>
<tr>
<td>RT given, BCS episodes only</td>
<td>1783</td>
<td>1963</td>
<td>2125</td>
<td>2217</td>
<td>2410</td>
<td>2681</td>
<td>3279</td>
<td>1.8% (1.0 to 2.6)</td>
</tr>
<tr>
<td></td>
<td>(65%)</td>
<td>(68%)</td>
<td>(70%)</td>
<td>(68%)</td>
<td>(70%)</td>
<td>(75%)</td>
<td>(77%)</td>
<td></td>
</tr>
<tr>
<td>RT given, mastectomy episodes only</td>
<td>183</td>
<td>162</td>
<td>181</td>
<td>176</td>
<td>182</td>
<td>205</td>
<td>219</td>
<td>0.3% (-0.3 to 0.8)</td>
</tr>
<tr>
<td></td>
<td>(23%)</td>
<td>(20%)</td>
<td>(21%)</td>
<td>(22%)</td>
<td>(22%)</td>
<td>(22%)</td>
<td>(24%)</td>
<td></td>
</tr>
<tr>
<td>Proportion receiving chemotherapy</td>
<td>27%</td>
<td>26%</td>
<td>25%</td>
<td>25%</td>
<td>27%</td>
<td>28%</td>
<td></td>
<td>0.3% (-0.4 to 1.0)</td>
</tr>
</tbody>
</table>

* Modelled using simple linear regression
† BCS: Breast conserving surgery
‡ RT: Radiotherapy
Table 4-4: Predictors of waiting time for radiotherapy in the group not receiving chemotherapy

<table>
<thead>
<tr>
<th>Patient level predictors</th>
<th>Non-hierarchical modelling</th>
<th>Hierarchical modelling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% change in median waiting time* (95% CI)</td>
<td>% change in median waiting time* (95% CI)</td>
</tr>
<tr>
<td>1993 vs. 1992</td>
<td>4% (1 to 8%)</td>
<td>9% (2 to 16%)</td>
</tr>
<tr>
<td>1994 vs. 1992</td>
<td>10% (7 to 13%)</td>
<td>10% (1 to 21%)</td>
</tr>
<tr>
<td>1995 vs. 1992</td>
<td>4% (1 to 8%)</td>
<td>5% (-8 to 20%)</td>
</tr>
<tr>
<td>1996 vs. 1992</td>
<td>9% (6 to 13%)</td>
<td>12% (0 to 24%)</td>
</tr>
<tr>
<td>1997 vs. 1992</td>
<td>17% (14 to 21%)</td>
<td>14% (-4 to 37%)</td>
</tr>
<tr>
<td>1998 vs. 1992</td>
<td>19% (8 to 31%)</td>
<td>63% (35 to 97%)</td>
</tr>
<tr>
<td>Regional cancer stage</td>
<td>9% (7 to 12%)</td>
<td>9% (4 to 14%)</td>
</tr>
<tr>
<td>For mastectomy vs. breast conserving surgery</td>
<td>16% (12 to 20%)</td>
<td>25% (15 to 36%)</td>
</tr>
<tr>
<td>If seen pre-op by a radio-oncologist</td>
<td>-16% (-20 to -11%)</td>
<td>-30% (-37 to -23%)</td>
</tr>
<tr>
<td>If surgery done in a centre where there is a radiotherapy service</td>
<td>-14% (-16 to -12%)</td>
<td>-13% (-17 to -8%)</td>
</tr>
<tr>
<td>Living more than 100 km from RT centre</td>
<td>15% (12 to 18%)</td>
<td>10% (4 to 17%)</td>
</tr>
<tr>
<td>missing information for living distance</td>
<td>n.a.</td>
<td>-5% (-34 to 35%)</td>
</tr>
<tr>
<td>At least 2/3 in household finished high-school</td>
<td>-2% (-4 to 0%)</td>
<td>-3% (-5 to -1%)</td>
</tr>
<tr>
<td>missing information for household education</td>
<td>-20% (-32 to -4%)</td>
<td>-53 to 39%</td>
</tr>
</tbody>
</table>

hospital level predictors:
Proportion of patients from high median income area, per 10% increase 

<table>
<thead>
<tr>
<th></th>
<th>Non-hierarchical modelling</th>
<th>Hierarchical modelling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n.a.</td>
<td>-2% (-3 to -1%)</td>
</tr>
</tbody>
</table>

* Calculated as [exp(coefficient from linear regression analysis of natural logarithm of waiting time) - 1] * 100, overall median waiting time was 66.9 days.

n.a.: not applicable, CI: confidence interval, RT: radiation therapy.
Table 4-5: Predictors of waiting time for radiotherapy in the group receiving chemotherapy between surgery and radiotherapy

<table>
<thead>
<tr>
<th>Patient level predictors</th>
<th>Non-hierarchical modelling</th>
<th>Hierarchical modelling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% change in median waiting time* (95% CI)</td>
<td>% change in median waiting time* (95% CI)</td>
</tr>
<tr>
<td>1993 vs. 1992</td>
<td>-1% (-13 to 13%)</td>
<td>5% (-10 to 23%)</td>
</tr>
<tr>
<td>1994 vs. 1992</td>
<td>-4% (-16 to 9%)</td>
<td>-5% (-27 to 24%)</td>
</tr>
<tr>
<td>1995 vs. 1992</td>
<td>2% (-10 to 16%)</td>
<td>-3% (-29 to 31%)</td>
</tr>
<tr>
<td>1996 vs. 1992</td>
<td>19% (5 to 35%)</td>
<td>25% (-14 to 82%)</td>
</tr>
<tr>
<td>1997 vs. 1992</td>
<td>25% (11 to 40%)</td>
<td>19% (-17 to 72%)</td>
</tr>
<tr>
<td>1998 vs. 1992</td>
<td>38% (23 to 55%)</td>
<td>35% (-3 to 88%)</td>
</tr>
<tr>
<td>Regional cancer stage</td>
<td>35% (27 to 43%)</td>
<td>28% (15 to 43%)</td>
</tr>
<tr>
<td>For mastectomy vs. BCS</td>
<td>34% (21 to 47%)</td>
<td>31% (16 to 48%)</td>
</tr>
<tr>
<td>If surgery done in a centre where there is a radiotherapy service</td>
<td>-21% (-26 to -15%)</td>
<td>-18% (-35 to 4%)</td>
</tr>
</tbody>
</table>

* Calculated as \[\exp(\text{coefficient from linear regression analysis of natural logarithm of waiting time}) - 1\]*100, overall median waiting time was 15.1 days.

CI: confidence interval, BCS: breast conserving surgery, RT: radiation therapy.
Figures

Figure 4-1: Examples of radiation therapy initiation date assignments

Episode 1 is accepted in the absence of a verification film code because it contains BOTH a simulation/dosimetry code AND a post-treatment visit code, it would have been rejected otherwise (as in example 2)

Episode 3 and 4 are automatically accepted because of the presence of a verification film code.
Figure 4-2: Definitions of waiting time

- surgery
- chemotherapy
- radiation therapy

patients without chemotherapy between surgery and radiation
patients with chemotherapy between surgery and radiation
Figure 4-3: Mean waiting time for radiation therapy, by calendar year for groups with and without chemotherapy. Vertical bars represent the 95% confidence intervals. Median waiting time for radiation therapy by calendar year.
Figure 4-4: Proportion of variation in waiting times explained by the available data for both groups
Figure 4-5: Distribution of the unadjusted proportion of patients waiting for specific durations for radiation therapy in the group of subjects who did not have chemotherapy between surgery and radiation by calendar year.