Report

A population-based study of the impact of delaying radiotherapy after conservative surgery for breast cancer

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Summary

Background. Practice guidelines have set a maximum waiting time to radiation therapy for breast cancer. We evaluated if delaying radiotherapy resulted in worse outcomes in a large cohort of women with node-negative breast cancer.

Methods. We selected a random sample of cases among women diagnosed with localized breast cancer in five regions of Québec, Canada, between 1988 and 1994. Only women with pathologically ($n=926$) or clinically ($n=136$) negative axillary nodes, and stage 1 or 2 disease treated with conservative surgery and radiotherapy were eligible. Information was obtained by chart review, queries to physicians and linkage with administrative databases. Outcomes were estimated by Kaplan–Meier method and Cox proportional hazards analysis. Median follow-up was 7.1 years (range: 0.9–11.8).

Results. Median delay to radiotherapy was 12.4 weeks in those who received chemotherapy and 8.4 weeks in others. Overall survival at 7 years was 85.6%. Local relapse-free and distant disease-free survivals were 77.6 and 76.2%. There was no significant difference in survival according to delay to radiotherapy in crude or multivariate analysis adjusting for several prognostic factors, including systemic treatment. The risk of local failure conditional on survival in women who received radiotherapy more than 12 weeks after surgery was increased (hazard ratio: 1.75, 95% confidence interval: 1.00, 3.08, p -value=0.052).

Conclusions. Although longer waiting time to radiotherapy may compromise local control, it does not influence survival at 7 years when other predictors of outcomes are taken into account. Well controlled studies are needed to confirm and better characterize this relationship.

Introduction

Radiation therapy following conservative surgery for breast cancer improves local control [1–3] and has been shown to favorably influence survival [4–7]. Additional analysis of the 36 randomized trials included in the Early Breast Cancer Trialists' Collab-

orative group meta-analysis that first reported this latter association showed that in recent and large trials, the odds reduction of death from any cause at 10 years associated with radiotherapy was 12.4% [8]. Alternatives to breast irradiation have been investigated, but it still represents the standard of care, even in women with very small tumors [9, 10].

With increasing demand for radiation therapy as more cases of cancer are diagnosed, due to aging of the population and intensified screening for cancer, and with recent changes in medical practice, access to radiotherapy facilities has been made more difficult in some jurisdictions. A focus of investigation has therefore been to identify shorter, more intensive regimens, having similar efficacy as the standard 25-day fractionation schedule [11], including partial breast irradiation strategies. In addition, the question of whether delaying radiotherapy has or not a detrimental effect on outcomes has become more relevant. Practice guidelines recommend a maximum waiting time to radiotherapy of 8–12 weeks, except in women undergoing chemotherapy [9]. Although theoretical models of breast tumor progression suggest an increase in relapse associated with longer delay to treatment [12, 13], the clinical basis of this observation is missing. The vast majority of studies on delay to radiation in women with breast cancer have shown little or no association with outcomes [14, 15]. However, a recent meta-analysis of eight observational studies led to a pooled random effects estimate of the odds ratio (OR) for local recurrence of 1.62 (95% confidence interval (CI): 1.21–2.16) among women treated between 9 and 16 weeks after surgery compared to those who had radiotherapy earlier [16]. Since no significant heterogeneity was observed across studies, no further adjustment was performed. The association with distant metastasis, as estimated by the pooling of three studies, was not significant. None of the reviewed studies reported on overall survival.

We used data collected on a large cohort of women diagnosed with node-negative breast cancer in Québec, Canada, between 1988 and 1994, and followed until the end of 1999, to evaluate the relationship between delay to radiotherapy and the risk of local or distant recurrence and death. Given the methodological limitations of published studies and evolving patterns of adjuvant systemic treatment in women with early-stage breast cancer, additional study of this issue would be useful.

Materials and methods

Study population

The sampling procedure and study population have been described [17]. Briefly, 1727 women

newly diagnosed with node-negative breast cancer in 1988–1989, 1991–1992 and 1993–1994 and living in five health regions (Montréal, Laval, Montérégie, Chaudière/Appalaches, Québec) of Québec were identified from the province-wide tumor registry (QTR) and hospital discharge databases, after exclusion of those with multiple primary, multicentric or inflammatory tumors, or lost to follow-up immediately after treatment. The current analysis was restricted to individuals with invasive breast cancer treated by conservative surgery and radiation therapy. Four women with missing information on prescription of chemotherapy were excluded, as well as 24 others with incomplete information on dates of radiotherapy. The final sample included 1062 women. The project was approved by the Commission d'accès à l'information du Québec, the directors of professional services in all hospitals, and research ethics committees.

Data collection

Information was collected by review of medical charts, including radiation oncology records. This was done twice, first in 1995–1996 to obtain details on disease at diagnosis and treatment of the primary tumor, then 5 years later to document recurrences and deaths. Patients having multiple admissions over time in several hospitals were identified from the QTR longitudinal database and all charts were reviewed. In addition, queries were made to the attending physicians to complete information on prescription of tamoxifen and outcomes of disease. Co-morbidity was estimated from a maximum of 15 secondary diagnoses listed in the hospital discharge summary of the first admission for treatment of breast cancer. This approach has shown better performance in predicting 1-year mortality than medication-based chronic disease scores [18]. Vital status was confirmed by linkage with the mortality database, the QTR and the database on beneficiaries of the Québec universal health insurance system (RAMQ). The RAMQ personal identifier was used for linkage, supplemented by the name at birth, surname, sex and date of birth for solving uncertain matches. RAMQ also identified individuals having moved out of the province before the end of follow-up on December 31, 1999.

Study variables

Information was collected on the patient, the physician and hospital of primary care, the tumor and details of treatments received within 6 months from diagnosis for chemotherapy and 12 months for radiotherapy and tamoxifen. Charlson's co-morbidity index [19] was calculated using the method described by Deyo [20]. Staging used criteria of the 4th edition of the American Joint Committee on Cancer [21]. We collected tumor size at pathology whenever available, otherwise size at mammography or clinical palpation. The highest value of grade assigned to a given tumor was used in the analysis. We combined women with missing value of lymphatic/vascular infiltration with those without infiltration. Delay to radiation was calculated as the interval between the first surgery with curative intent and the first session of radiation therapy. Data were also collected on first recurrences and second primary tumors, including dates of diagnosis and treatment. Because of the lack of central pathology review, we combined local recurrences in the mammary gland, chest wall or surgery scar with ipsilateral second breast primaries in the definition of ipsilateral breast tumor recurrences (IBTR). Second breast primaries were therefore restricted to tumors in the contralateral breast. Regional recurrences were located in ipsilateral axillary nodes, internal mammary chain, infra- or supra-clavicular nodes or soft tissues of the axilla. Distant recurrences were those in the contralateral axillary, internal mammary or infra- or supra-clavicular nodes, as well as in distant sites.

Definition of outcomes

Two indicators were used to evaluate local control. The first one, local failure-free conditional on survival, included IBTR as event but censored on all other outcomes, including death. The second indicator, local relapse-free survival, counted both IBTR and death as events, and censored on regional or distant recurrence and second primary tumor.

Events included in the computation of distant-disease free survival were regional or distant recurrence, second primary tumor, or death; women with local failure as first event were censored at the date of this occurrence. Finally,

overall and breast cancer specific survivals included all-cause or breast cancer specific deaths.

Data analysis

The associations between delay to radiotherapy and other determinants of outcomes were tested using the Pearson's χ^2 test. Survival analysis was done using Kaplan–Meier estimates and Cox proportional hazards models of each end-point defined above. Time under follow-up was computed from the date of pathological diagnosis. It was censored at the last medical consultation in the analysis of recurrences. Women who moved out of the province were censored at the date of moving.

Kaplan–Meier estimates of survival according to delay to radiotherapy were compared by the log-rank test. Survival rates and their 95% CI at specific years after diagnosis were estimated. Cox proportional hazards models used as main independent variable delay to radiotherapy, and included several prognostic or predictive factors, such as age, co-morbidity, tumor stage, grade, estrogen receptor (ER) status, lymphatic/vascular infiltration, margin status, as well as details of treatment such as dissection of the axilla, tamoxifen, chemotherapy and total dose of radiation to the breast. In all models, the proportionality assumption was verified both graphically and by maximum likelihood estimation using time-dependent covariates and goodness-of-fit was assessed by residual analysis. A 5% level of statistical significance was used and all tests were bilateral.

Results

Description of the study population

Table 1 summarizes the main characteristics of the 1062 women under study. The majority were less than 65 years old, had stage 1 disease and no significant co-morbidity. Tumors were grade 1 or 2 in 41.9%, ER-positive in 58.1%, and 8.9% had some mention of lymphatic or vascular infiltration at pathology. Margin infiltration was reported in 17.8% of all cases following the last surgery. Absence of regional extension was determined either at pathology ($n=926$) or clinically ($n=136$). With regard to systemic treatment, 20.4% of these individuals received some chemotherapy, and

Table 1. Description of the study population

Variable	n	%
Age, years		
<65	749	70.5
≥65	313	29.5
Co-morbidity index		
0	990	93.2
≥1	70	6.6
Missing	2	0.2
Delay to radiation therapy, weeks		
≤8	452	42.6
8–12	319	30.0
>12	291	27.4
Assessment of axillary nodes		
Pathology	926	87.2
Clinical	136	12.8
Tamoxifen		
Yes	574	54.0
No	420	39.5
Protocol tamoxifen versus placebo ^a	68	6.4
Chemotherapy		
Yes	217	20.4
No	845	79.6
Tumor stage		
1	773	72.8
2	289	27.2
Grade		
1–2	445	41.9
3	286	26.9
Missing	331	31.2
Er status		
Positive	617	58.1
Negative	275	25.9
Missing	170	16.0
Lymphatic/vascular infiltration		
Yes	95	8.9
No/missing	967	91.1
Margin status		
Tumor present	189	17.8
Tumor absent	689	64.9
Missing	184	17.3
Total	1062	100

^a Includes six women with missing information on tamoxifen.

54.0% were prescribed tamoxifen. Overall, 27.4% of the cohort received radiotherapy more than 12 weeks after breast-conserving surgery. The median interval to radiotherapy was 8.4 weeks

(mean: 9.3) among women who did not receive chemotherapy and 12.4 weeks (median 14.0) in those who did; maximum delay was 38 and 50 weeks, respectively.

Factors associated with delay to radiotherapy

To assess the importance of confounding by indication and the extent by which waiting time to radiotherapy could be influenced by prognosis at baseline, the distribution of delay to radiation according to several prognostic and predictive variables, as well as co-treatment, was evaluated separately among women who received or not chemotherapy (Table 2). Women having more co-morbidity were treated more rapidly, whether or not they received chemotherapy, but this relationship was only significant in those who did (χ^2 p -value = 0.035). The number of individuals who had a Charlson's index of one or more was however very small (10 and 60 in these two groups).

Women under experimental protocol involving tamoxifen or placebo ($n=62$) or with missing information on use of tamoxifen ($n=6$) who did not receive chemotherapy had substantially shorter delay to radiation, as expected, 66% being treated within 8 weeks, as compared to 44.8% and 47.1% of those with or without prescription of tamoxifen who did not participate to clinical research. Otherwise, delay to radiation was not influenced by the fact that a woman had a prescription of tamoxifen, a dissection of the axilla, or by the total dose of radiation delivered to the breast.

No significant association with age, tumor stage, grade, ER status, lymphatic/vascular or margin infiltration was observed among women with known values of these variables, although those with missing information, especially on tumor grade, ER and margins, often experienced different waiting times to radiotherapy. For example, in women who received chemotherapy, 37.5% of women with grade missing, 56.9% of those with grade 1/2 and 53.6% of women with grade 3 tumors were treated more than 12 weeks after surgery. The same trend was observed in individuals who did not receive cytotoxic treatment.

Outcomes according to delay to radiotherapy

During a median follow-up of 7.1 years (range: 0.9–11.8 years), 182 women died, 90 of breast

Table 2. Delay to radiation therapy according to selected variables

Variable	Delay in women without chemotherapy, weeks (<i>n</i> = 845)				Delay in women with chemotherapy, weeks (<i>n</i> = 217)			
	≤8 %	8–12 %	>12 %	<i>p</i> -Value	≤8 %	8–12 %	>12 %	<i>p</i> -Value
Age, years								
<65	44.8	33.1	22.1	0.223	25.7	23.8	50.5	0.461
≥65	51.0	29.5	19.5		20.0	13.3	66.7	
Co-morbidity index								
0	46.6	31.3	22.1	0.087	23.7	23.7	52.7	0.035
>0	53.3	36.7	10.0		60.0	10.0	30.0	
Dissection of axilla								
Yes	47.5	31.7	20.8	0.654	26.5	24.0	49.5	0.160
No	43.4	32.7	23.9		14.3	14.3	71.4	
Tamoxifen								
Yes	44.8	32.1	23.1	0.715 ^a	22.3	20.2	57.4	0.231 ^a
No	47.1	32.1	20.8		28.7	25.9	45.4	
Protocol tamoxifen vs placebo ^b	66.0	28.3	5.7		20.0	20.0	60.0	
Radiation dose, Gy								
≤50	47.2	31.8	21.0	0.710	26.5	22.5	51.0	0.341
>50	42.1	31.6	26.3		8.3	33.3	58.3	
Tumor stage								
1	45.9	32.0	22.1	0.394	26.1	27.0	46.8	0.270
2	50.8	31.1	18.0		24.5	18.9	56.6	
Grade								
1–2	42.4	34.5	23.2	0.560 ^c	27.7	15.4	56.9	0.084 ^c
3	38.5	34.5	27.0		17.9	28.6	53.6	
Missing	58.1	26.8	15.1		42.5	20.0	37.5	
Er status								
Positive	49.0	32.1	18.8	0.414 ^c	24.2	26.4	49.5	0.739 ^c
Negative	52.7	26.7	20.6		24.5	21.8	53.6	
Missing	33.8	36.4	29.9		37.5	12.5	50.0	
Lymphatic/vascular infiltration								
Present	42.2	40.6	17.2	0.281	32.3	25.8	41.9	0.482
Absent/missing	47.4	31.1	21.5		24.2	22.6	53.2	
Margin status								
Tumor present	45.3	28.1	26.6	0.446 ^c	24.0	32.0	44.0	0.188 ^c
Tumor absent	45.4	32.4	22.2		25.7	19.7	54.6	
Missing	53.3	33.1	13.6		26.7	26.7	46.7	
Total	397	269	179	845	55	50	112	217

n – number.

^a Comparison excludes women under protocol or with missing information on tamoxifen.

^b Including 6 women with missing information on tamoxifen.

^c Comparison excludes women with missing value.

cancer. There were 89 local failures, 35 regional recurrences, 135 distant recurrences, 38 second breast primaries and 52 second primary tumors in the cohort.

Patterns of recurrence did not differ according to waiting time to radiotherapy in crude analysis (Table 3). The probability of being free of local failure at 7 years, conditional on survival, was

Table 3. Estimates of survival at 7 years according to delay to radiotherapy

	Outcomes							
	<i>n</i>	% Local failure-free conditional on survival (95% CI)	<i>n</i>	% Local relapse-free survival (95% CI)	<i>n</i>	% Distant disease-free survival (95% CI)	<i>n</i>	% Overall survival (95% CI)
<i>All women</i>	392	90.6 (88.5, 92.7)	403	77.6 (74.8, 80.4)	395	76.2 (73.4, 79.1)	532	85.6 (83.4, 87.7)
Delay to radiotherapy, weeks								
≤8	223	91.6 (88.7, 94.4)	230	77.6 (73.5, 81.7)	224	75.8 (71.6, 80.1)	293	84.7 (81.3, 88.0)
8–12	106	91.7 (88.0, 95.4)	108	78.3 (73.1, 83.5)	108	76.4 (71.1, 81.7)	148	85.5 (81.3, 89.7)
>12	63	87.1 (82.1, 92.0)	65	76.2 (70.4, 81.9)	63	76.7 (71.0, 82.3)	91	86.8 (82.8, 90.8)
<i>Women with chemotherapy</i>	84	90.2 (85.7, 94.7)	86	78.0 (72.1, 83.9)	84	76.2 (69.9, 82.5)	110	86.2 (81.5, 90.9)
Delay to radiotherapy, weeks								
≤8	32	87.7 (78.4, 97.0)	34	75.8 (64.3, 87.3)	33	78.4 (67.0, 89.8)	40	85.2 (75.7, 94.7)
8–12	16	97.9 (93.9, 102.0)	16	82.4 (71.2, 93.6)	15	70.6 (56.1, 85.1)	20	83.6 (73.2, 94.0)
>12	36	87.9 (80.6, 95.1)	36	77.5 (69.0, 85.9)	36	78.1 (69.5, 86.7)	50	88.1 (82.0, 94.2)
<i>Women without chemotherapy</i>	308	90.7 (88.3, 93.0)	317	77.5 (74.3, 80.6)	311	76.3 (73.1, 79.5)	422	85.4 (82.9, 87.9)
Delay to radiotherapy, weeks								
≤8	191	92.1 (89.1, 95.1)	196	77.8 (73.5, 82.2)	191	75.5 (71.0, 80.0)	253	84.6 (81.1, 88.2)
8–12	90	91.6 (87.7, 95.5)	92	77.6 (71.8, 83.4)	93	77.5 (71.9, 83.2)	128	85.9 (81.4, 90.4)
>12	27	85.9 (78.6, 93.2)	29	74.6 (66.5, 82.7)	27	75.9 (68.6, 83.2)	41	85.9 (80.6, 91.3)

CI – confidence interval; *n* – number of women at risk at 7 years.

90.6% and varied little with delay to radiotherapy (log-rank test: 1.78, *p*-value: 0.411), both in women who received or not chemotherapy. Kaplan–Meier estimates of local relapse-free and distant disease-free survivals were 77.6 and 76.2%. Again, these outcomes were similar across categories of waiting time to radiotherapy (log-rank tests: 0.08, *p*-value: 0.959 and 0.35, *p*-value: 0.840).

For the whole cohort, the 7-year estimate of overall survival was 85.6% (Table 3) and was similar in women who received radiotherapy within 8 weeks, 8–12 weeks, or more than 12 weeks after surgery (84.7, 85.5 and 86.8%, log-rank test: 0.66, *p*-value: 0.719). Breast cancer specific survival was 92.0% and displayed the same lack of association with delay in crude analysis (91.3, 93.4 and 91.4%, log-rank test: 1.84, *p*-value: 0.399).

Results of multivariate analyses are summarized in Table 4. In most models, waiting time to radiotherapy was not a significant predictor of outcome

after adjustment for other covariates, including systemic treatment received. Hazard ratios (HR) of death from any cause were 0.92 (95% CI: 0.65, 1.30) and 0.93 (95% CI: 0.62, 1.39) in individuals treated 8–12 weeks, and more than 12 weeks after surgery, compared to those treated within 8 weeks. For deaths specific to breast cancer, they were 0.75 (95% CI: 0.44, 1.28) and 0.94 (95% CI: 0.55, 1.61), respectively. Women who started radiotherapy more than 12 weeks after breast-conserving surgery were at increased risk for local failure conditional on survival, and this was of borderline significance (HR: 1.75, 95% CI: 1.00, 3.08, *p* = 0.052). This excess risk was mostly concentrated in the subgroup of women who did not receive chemotherapy (HR: 1.91, 95% CI: 1.00, 3.64, *p* = 0.049), but was not observed among those who did (HR: 0.97, 95% CI: 0.31, 3.10, *p* = 0.962). An interaction term between margin status and delay to radiotherapy was not significant in any model.

Table 4. Multivariate Cox analysis of delay to radiation therapy and outcomes of breast cancer ($n = 1004$)

Delay to radiotherapy, weeks	Events							
	n	Local recurrence	n	Local recurrence or death	n	Regional/distant recurrence, second primary or death	n	Death from any cause
		HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)
≤ 8	34	1.0	112	1.0	124	1.0	88	1.00
8–12	24	1.22 (0.71, 2.08)	68	1.02 (0.75, 1.38)	74	0.96 (0.72, 1.29)	51	0.92 (0.65, 1.30)
> 12	27	1.75 (1.00, 3.08)	61	1.19 (0.85, 1.67)	59	0.96 (0.69, 1.35)	40	0.93 (0.62, 1.39)

n – number of events in category.

HR – hazard ratio.

NB – estimates are adjusted for age, co-morbidity, dissection of the axilla, dose of radiation to the breast, tumor stage, grade, ER status, lymphatic/vascular infiltration, margin infiltration and systemic adjuvant treatment (none, chemotherapy only, tamoxifen only, both).

Discussion

In our review [14] of published studies [15, 22–40] on delay in adjuvant radiation treatment and outcomes of breast cancer, we explored the reasons, methodological or others, for inconsistencies in this literature. Four of these investigations [27–30] included only patients who did not receive chemotherapy; none suggested a detrimental effect of longer delay to radiotherapy after adjustment for covariates. By contrast, four [22, 34, 35, 40] of 12 studies [15, 22, 31–40] that included patients who did receive chemotherapy and often experienced waiting times to radiotherapy of 6 months or more showed a detrimental effect of longer delay, especially on local control, a result consistent, to some extent, with two [26, 41] published randomized studies on sequencing, but not with a third one [42]. It is possible that the impact of delaying radiation therapy would be different in node-negative and positive patients. Whelan et al.'s meta-analysis of trials of radiotherapy in patients with chemotherapy [6] also showed a significant decrease in mortality among patients treated within 6 months of starting chemotherapy (OR for mortality: 0.78, 95% CI: 0.69, 0.89). Two randomized clinical trials of alternative chemotherapy regimens [31, 32] that provided indirect evidence on the issue of delay to radiation were included in our review, but were negative with respect to this specific hypothesis. Overall, and given the observational nature of the majority of these studies, limitations were identified for several of them, including small sample size, short period

of follow-up, lack of proper adjustment for significant prognostic factors, especially margin status which could act as a confounder or a modifier of the effect of delay to radiation, and failure to account for systemic treatment, including tamoxifen. These adjustments are critical, since confounding by indication and selective referral of patients to prompt or late treatment according to their estimated risk of recurrence is plausible. Such selective referral may be more likely in a context where access to care has to be rationalized.

Our series together with the study by Froud et al. [30] which included 1962 patients treated in British Columbia between 1989 and 1993, 80% of whom were node-negative, represent the largest series of women with node-negative breast cancer investigated to date. Although, as expected, waiting time was longer in patients who received chemotherapy, we did not observe in crude analysis evidence that referral was influenced by determinants of risk of recurrence such as age, tumor grade, ER or margin status, or prescription of tamoxifen in women for whom this information was available. There was a trend for earlier treatment in individuals with more co-morbidity. The reasons why women with missing values about tumor grade, ER receptors or margin infiltration had different patterns of treatment are unclear, apart from the fact that missing information was more common in small tumors during the period our cases were diagnosed. Tendency to treat these women faster or later could therefore exaggerate or attenuate the effect of delay. We did control in our multivariate models for all prognostic and

predictive factors, including co-morbidity and adjuvant systemic treatment, likely to act as confounders of the delay-outcome relationship.

Like Paszat et al. [43], we used two different indicators to evaluate local control. Differences between them comes from the inclusion of death as either an outcome or a censoring event. Although longer delay did not result in a reduction of local relapse-free survival, there was an increased hazard ratio of local failure conditional on survival with longer time to radiotherapy, of marginal significance in the group with longer delay (>12 weeks). Both definitions of local failure should be considered in the assessment of delay to radiotherapy, given the excess mortality, particularly vascular, reported in older trials of radiotherapy, especially after the first 2 years following randomization [5].

Delay to radiation therapy can be calculated from different baselines, including diagnosis, first or last curative surgery. Several published studies have calculated delay from the last surgery, whereas we used date of first surgical intervention. Taking into account, as we did, the time spent with residual disease between the first and last surgery is justified from a biological perspective, whereas calculating delay from the last surgery is more compatible with a rationale of services delivery. However, using the last instead of the first surgery would result in a downward shift in the distribution of our study population according to time to radiation and could attenuate any trend in risk with increasing time to radiotherapy. Thus, differences in the choice of baseline to calculate delay could partly explain variation in study findings.

Huang et al.'s [16] recent meta-analysis also suggests an excess of local failure in women treated later after surgery, but as we previously cautioned [44], this report has limitations. Some important relevant publications were omitted [23, 28, 31, 32, 39], whereas in others, some data were excluded from the summary estimates [33, 36, 37]. In addition, research results published only as abstracts were admissible and no meta-regression was performed on the basis of the lack of statistical significance of a test for heterogeneity across studies.

Our study has both strengths and limitations. First, it is population-based and did include approximately half of all new cases of node-negative breast cancer diagnosed in Québec during these years. Second, we were able to adjust for

several important covariates, including co-morbidity. Although the information from the medical records may have been incomplete or inaccurate, we tried to upgrade it by direct queries to the attending physicians. This procedure is likely to have minimized misclassification of some variables, especially tamoxifen. In addition, the study population was homogeneous with regard to the extent of disease at diagnosis and the surgical approach used. On the other hand, we had no information on functional status, a factor that could influence both access to care and its outcomes, and follow-up was relatively short given the low risk of recurrence of these cases. Finally, quality of life was not included among the outcomes and could vary substantially with waiting time to treatment.

In conclusion, we observed that delaying radiation therapy following conservative surgery for localized breast cancer was associated with a small marginally significant increase in the risk of local failure conditional on survival, but did not influence other outcomes of treatment, including survival. Indirect evidence provided by randomized clinical trials of chemotherapy should be pooled and more well designed observational studies conducted to clarify this relationship.

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