Adjuvant radiotherapy for early breast cancer: patterns of practice in Ontario

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Objective: To determine the number of different radiation schedules used in Ontario to treat women with node-negative breast cancer after lumpectomy and axillary dissection.
Design: Retrospective survey.
Setting: Princess Margaret Hospital, Toronto, and regional centres of the Ontario Cancer Treatment and Research Foundation (in Hamilton, London, Ottawa, Windsor and Thunder Bay).
Patients: A total of 551 of 1624 consecutive patients with node-negative breast cancer having undergone lumpectomy and axillary dissection who were eligible but did not participate in the Ontario Clinical Oncology Group randomized clinical trial and who received adjuvant breast irradiation between April 1984 and February 1989.
Outcome measures: Schedules of radiotherapy received.
Results: Forty-eight different radiotherapy schedules were identified. Total doses ranged from 4000 to 6600 cGy and the number of fractions from 15 to 30. Several different schedules were preferred: 322 patients (58.5%) received 4000 cGy in 15 or 16 fractions to the whole breast over 3 weeks plus a local boost of 1250 cGy to the primary site in 5 fractions over 1 week; 66 patients (12.0%) received 4000 cGy in 15 or 16 fractions over 3 weeks to the whole breast plus a local boost of 1000 cGy to the primary site in 4 or 5 fractions over 1 week; and 63 patients (11.5%) received 5000 cGy in 25 fractions to the whole breast in 5 weeks, without a boost.
Conclusions: The practice of adjuvant radiotherapy for early breast cancer in Ontario varies. The optimal radiation regimen for patients after lumpectomy should be determined through randomized clinical trials.

Objectif : Déterminer le nombre des différents calendriers radiques utilisés en Ontario pour traiter des femmes ayant un cancer du sein sans atteinte aux ganglions, après exérèse locale et curage axillaire.
Conception : Enquête rétrospective.
Contexte : Hôpital Princess Margaret, Toronto, et les centres régionaux de la Fondation ontarienne pour la recherche en cancérologie et le traitement du cancer (à Hamilton, London, Ottawa, Windsor et Thunder Bay).
Patientes : Un total de 551 sur 1 624 patientes consécutives ayant un cancer du sein sans atteinte aux ganglions, ayant subi une exérèse locale et curage axillaire, qui étaient admissibles à l'essai clinique randomisé du Groupe d'oncologie clinique de l'Ontario, mais n'y ont pas

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participé, et ont reçu un traitement d'appoint par irradiation entre avril 1984 et février 1989.
Mesures des résultats : Calendriers des radiothérapies reçues.
Résultats : Quarante-huit calendriers différents de radiothérapie ont été recensés. Les doses totales allaient de 4 000 à 6 600 cGy et le nombre de fractions, de 15 à 30. Plusieurs calendriers différents avaient la préférence : 322 patientes (58,5 %) ont reçu 4 000 cGy en 15 ou 16 fractions au sein entier, sur une période de 3 semaines, plus un rappel local de 1 250 cGy sur le site principal en 5 fractions, en une semaine; 66 patientes (12,0 %) ont reçu 4 000 cGy en 15 ou 16 fractions, au sein entier, sur une période de 3 semaines, plus un rappel local de 1 000 cGy au site principal en 4 ou 5 fractions, en une semaine; et 63 patientes (11,5 %) ont reçu 5 000 cGy en 25 fractions, au sein entier, en 5 semaines, sans rappel.
Conclusions : La pratique en Ontario varie pour ce qui est de la radiothérapie d'appoint dans le traitement du cancer précoce du sein. Les schémas radiques optimaux pour les patientes ayant subi une exérèse locale devraient être déterminés par des essais cliniques randomisés.

Conservative surgery in the treatment of early breast cancer has become increasingly popular since the publication of several clinical trials in the early 1980s showing comparable results of such surgery compared with those of mastectomy.[1-4] Clinical trials have also demonstrated that breast irradiation after lumpectomy reduces the risk of recurrence of cancer in the treated breast.[3-6] Thus, breast irradiation is now considered standard treatment after lumpectomy.[7] With the increasing use of screening mammography more cases of early breast cancer amenable to this therapy are being discovered. The result has been an increased demand on centres providing radiotherapy. With this increasing caseload the ability to deliver timely breast irradiation is becoming more difficult, and the result is long waiting lists for patients.

Several different radiation schedules were used in the randomized trials and cohort studies that evaluated the role of adjuvant breast irradiation.[1-6,8-10] Indeed, three national surveys of clinical practice in Britain, France and the United States identified variations in the radiation schedules used to treat patients after lumpectomy.[11-13] The reason for this remains unexplained, but regional preference and physician choice are involved in part.[11] The lack of randomized trials comparing radiation schedules has no doubt contributed to the variability observed.

In view of the difficulty in meeting the increased demand for adjuvant breast radiotherapy in Ontario it was considered important to examine patterns of practice. We report the results of a study of the radiation schedules used to treat eligible patients who did not consent to be enrolled in a randomized trial of local breast irradiation in women with node-negative breast cancer.[6]

Methods

Between April 1984 and February 1989 a randomized trial of local breast irradiation after lumpectomy and axillary dissection in women with node-negative breast cancer was conducted at a number of Ontario regional cancer centres by the Ontario Clinical Oncology Group (OCOG).[6] Participating centres included the Princess Margaret Hospital, Toronto, and regional centres of the Ontario Cancer Treatment and Research Foundation (in Hamilton, London, Ottawa, Windsor and Thunder Bay).

The study population included patients who had had lumpectomy and axillary dissection with a histologically confirmed diagnosis of invasive breast cancer without axillary node involvement. The tumours had to be 4 cm or less in diameter, with microscopically clear resection margins. Exclusion criteria included a history of surgery for breast cancer, evidence of skin infiltration in the involved breast (e.g., edema and ulceration), deep fixation to underlying muscle, pure ductal carcinoma in situ or lobular carcinoma in situ, bilateral breast cancer, more than one primary tumour in the same breast, a documented history of previous cancer (except squamous or basal cell carcinoma of the skin), serious nonmalignant systemic medical illness, underlying psychiatric or addictive disorders, a breast deemed too large to permit satisfactory radiation, receipt of any adjuvant systemic therapy, an inability to commence radiation within 12 weeks after surgery and geographic inaccessibility for follow-up.

Eligible patients who agreed to participate in the OCOG study were randomly assigned to receive adjuvant breast irradiation or no further treatment. Patients in the former group received 4000 cGy in 16 fractions to the whole breast over 3 weeks (actually 3 weeks and 1 day, since radiation was given daily Monday to Friday) followed by a local boost of 1250 cGy in 5 fractions to the primary site over 1 week.

Eligibility forms for all women considered for participation in the OCOG trial were completed by the treatment centres at the time of initial patient assessment. In addition to the information provided by these forms the treatment received by nonparticipating patients was obtained through a retrospective review of the patients' charts and radiotherapy prescriptions. One of the investigators visited each cancer centre and reviewed each chart. Approval for this review was obtained from each centre's local ethics committee.

A total of 1624 patients were deemed eligible and were approached for consent; 787 (48.5%) did not consent and form the basis of this report. No patients were lost to follow-up.

Since this retrospective review was based on treatment practices between 1984 and 1989 we surveyed the nine cancer centres in Ontario for their current recommended radiation schedule for women with node-negative breast cancer after lumpectomy with microscopically clear margins.

Results

Of the 787 patients who were not enrolled in the randomized trial, 551 received breast irradiation. Forty-eight different schedules were identified. One patient who did not complete treatment received 1000 cGy in four fractions and was excluded from the analysis. The total dose (the dose to the breast plus the local boost to the primary site) varied from 4000 to 6600 (median 5250) cGy (Table 1). The number of fractions per patient varied from 15 to 30 (median 21) (Table 2).

Sixteen separate schedules were used to treat the whole breast. The dose ranged from 3650 to 5000 cGy, given in 13 to 25 fractions. A total of 470 patients (85.5%) were treated with a local boost to the primary site; 17 different schedules were used. Only one patient received an interstitial implant as a boost: she received 2000 cGy following 4600 cGy in 23 fractions to the whole breast. The boost dose delivered by external beam therapy ranged from 500 to 1500 cGy in two to six fractions.

Despite the variation observed, certain schedules were preferred: 322 patients (58.5%) received 4000 cGy in 15 or 16 fractions to the whole breast over 3 weeks plus a local boost of 1250 cGy in 5 fractions to the primary site over 1 week; 66 patients (12.0%) received 4000 cGy in 15 or 16 fractions to the whole breast over 3 weeks plus a local boost of 1000 cGy in 4 or 5 frac-

Table 2: Total number of fractions per radiation schedule

Total no. of fractions	No. (and %) of patients
15	6 (1.1)
16	4 (0.7)
17	5 (0.9)
18	14 (2.5)
19	24 (4.4)
20	127 (23.1)
21	272 (49.5)
22	1 (0.2)
23	3 (0.5)
24	1 (0.2)
25	77 (14.0)
26	2 (0.4)
27	1 (0.2)
28	3 (0.5)
29	2 (0.4)
30	8 (1.5)

Table 1: Treatment received by 550 patients with node-negative breast cancer who underwent lumpectomy and axillary dissection from April 1984 to February 1989 in Ontario*

Total dose, cGy/ no. of fractions†	No. (and %) of patients	Total dose, cGy/no. of fractions†	No. (and %) of patients
4000/15	6 (1.1)	5100/20	1 (0.2)
4000/16	3 (0.5)	5200/18	2 (0.4)
4000/20	1 (0.2)	5250/16	1 (0.2)
4250/20	1 (0.2)	5250/18	1 (0.2)
4300/19	1 (0.2)	5250/20	72 (13.1)
4500/17	5 (0.9)	5250/21	250 (45.5)
4500/18	1 (0.2)	5250/25	1 (0.2)
4600/19	1 (0.2)	5250/26	1 (0.2)
4600/23	3 (0.5)	5500/20	2 (0.4)
4750/18	8 (1.5)	5500/21	2 (0.4)
4750/19	13 (2.4)	5500/27	1 (0.2)
4750/22	1 (0.2)	5750/28	2 (0.4)
4800/18	1 (0.2)	5800/29	1 (0.2)
4900/21	1 (0.2)	5880/30	1 (0.2)
4950/19	1 (0.2)	5900/28	1 (0.2)
5000/18	1 (0.2)	6000/26	1 (0.2)
5000/19	8 (1.5)	6000/29	1 (0.2)
5000/20	50 (9.1)	6000/30	7 (1.3)
5000/21	19 (3.5)	6250/25	1 (0.2)
5000/24	1 (0.2)	6600/24‡	1 (0.2)
5000/25	74 (13.5)		

*The patients were eligible for the Ontario Clinical Oncology Group randomized clinical trial but did not participate.
†Some patients had the same total dose and total number of fractions but received the treatment according to different schedules.
‡Patient was treated with interstitial implant of 2000 cGy after receiving 4600 cGy in 23 fractions to the whole breast.

tions to the primary site over 1 week; and 63 patients (11.5%) received 5000 cGy in 25 fractions to the whole breast over 5 weeks, without a boost.

Fifteen patients (2.7%) received additional regional irradiation: 5 received treatment to the internal mammary region only, through a parasternal field, and 10 received treatment to the supraclavicular and axillary regions.

Our survey of the cancer centres revealed six different recommended radiation schedules, ranging in doses from 4000 to 6000 cGy in 16 to 30 fractions (Table 3).

Discussion

Because of the increasing demands on cancer centres to provide adjuvant breast irradiation we attempted to gain information on the number of different treatment schedules used in Ontario. We found that treatment varied in the total dose and in the number of fractions. Given the variation identified, overall treatment time was likely to vary from 19 to 40 days. Despite this lack of uniformity, however, the schedule used in the randomized OCOG trial and that used in the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial of conservative surgery and adjuvant radiation (5000 cGy in 25 fractions)[3,4,6] were prescribed for a large proportion of patients in our retrospective study. When we examined current practice, the lack of consensus for a standard schedule was consistent with the variability we observed.

This variation in practice may be related in part to a perceived uniformity of outcome of several different schedules. Although there are limitations to cross-study comparisons the results of several randomized trials and cohort studies using different radiation regimens, some as short as 3 weeks, have demonstrated similar rates of local control and late morbidity.[1-6,8-10] The ultimate effect of a schedule may depend on a host of clinical and radiobiologic factors. Various methods have been used to predict the effect of modifying total dose, treatment time and fraction size: for example, nominal standard dose; time, dose and fractionation; and, more recently, biologic effective dose.[14,15] Unfortunately, such methods are limited. They are based on retrospective analyses and animal studies, and the effects of overall treatment time are not well known, especially for breast cancer.[16,17] In addition, clinical factors, such as the ability to localize the primary site for boost radiation, are not accounted for.[18] The most acceptable method to compare schedules would be direct comparison in a randomized trial with blinded assessment of outcome. Unfortunately, such studies have not been performed.

Table 3: Current recommended radiation schedules in Ontario cancer centres for node-negative breast cancer after lumpectomy with microscopically clear margins

Total dose, cGy/ no. of fractions	No. of centres*
4000/16	1
4400/16	1
4500/20	1
4000/16 + 1250/5	2
5000/25	4
5000/25 + 1000/5	1

*One centre recommended two schedules.

Variability in radiation schedules used to treat patients with node-negative breast cancer after lumpectomy is not peculiar to Ontario.[11-13] In 1989 the Royal College of Radiologists sent a questionnaire to 222 radiation oncologists practising in Britain: 51 different schedules were identified.[11] They ranged from 6 to 45 fractions given over 3 to 8 weeks. When questioned as to what influenced their choice of treatment, 90% of the radiation oncologists responded that local policy and previous training did. Only 30% attributed their choice to logistic restraints and less than 5% to results from clinical trials. Similar information from radiation oncologists in Ontario was not available from our study, but it would seem likely that the same factors would apply.

Unlike the Royal College survey, we recorded the treatments patients actually received rather than what physicians reported their practice to be. Some of the variation we observed may be related to incompletion of planned therapy. However, this factor is unlikely to have had a significant effect, because the acute side effects of treatment are minimal. Another source of variability may be related to technical factors such as breast size and dose inhomogeneity. A potential limitation of our study is that by its design it was limited to patients who did not consent to participate in a randomized trial and may not be representative of everyday practice. Although nonconsenting patients have been shown in some circumstances to behave differently than consenting patients it is difficult to conceive that this might affect the radiation treatment they received in this study.

Conclusion

This retrospective study demonstrated variation in the practice of adjuvant radiotherapy for early breast cancer in Ontario. A comparison of findings from randomized controlled trials and cohort studies suggest that several schedules may have similar outcomes. Given the clear evidence of therapeutic effectiveness of adjuvant radiation in reducing the rate of local recurrence and avoiding mastectomy as well as the increasing inability of the health care system to meet the clinical demand for radiation treatment, it would seem reasonable to try to identify the most effective and efficient radiation schedule. If it could be clearly demonstrated in a randomized trial that a shorter schedule (e.g., 3 weeks) was as effective as a longer schedule (e.g., 4 to 5 weeks), in terms of

tumour control and late morbidity, there would be obvious advantages. If the overall duration of treatment were shortened, patient convenience would be increased and more patients could be treated with the available resources.

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