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SHORT COMMUNICATION

Tumour response 3 months after neoadjuvant single-fraction radiotherapy for low-risk breast cancer

D. Tiberi MD,* P. Vavassis MD,* D. Nguyen MD,* M.C. Guilbert MD,† A. Simon-Cloutier MD,‡ P. Dubé MD,‡ M.K. Gervais MD,‡ L. Sideris MD,‡ G. Leblanc MD,‡ T. Hijal MD,§ M.P. Dufresne MD,‖ and M. Yassa MD*

ABSTRACT

Introduction Standard treatment for early-stage invasive breast cancer (BCa) consists of breast-conserving surgery and several weeks of adjuvant radiotherapy (RT). Neoadjuvant single-fraction RT is a novel approach for early-stage BCa. We sought to investigate the effect of delaying surgery after neoadjuvant RT with respect to the rate of pathologic response (pR).

Methods Women 65 years of age or older with a new diagnosis of stage I luminal A BCa were eligible for inclusion. A single 20 Gy dose to the primary breast tumour was given, followed by breast-conserving surgery 3 months later. The primary endpoint was the pR rate assessed by microscopic evaluation using the Miller–Payne system.

Results To date, 10 patients have been successfully treated. Median age of the patients was 72 years (range: 65–84 years). In 8 patients, neoadjuvant RT resulted in a tumour pR with median residual cellularity of 3%. No immediate RT complications other than mild dermatitis were noted.

Conclusions This study demonstrates a method for delivering single-fraction RT that can lead to a high level of pR in most patients. Continued accrual to this study and subsequent trials are needed to determine the feasibility, safety, and role of this novel technique in the management of early-stage BCa.

Key Words Breast cancer, preoperative radiotherapy, SBRT, SABR, radiosurgery, ablative radiotherapy

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INTRODUCTION

Standard treatment for early-stage invasive breast cancer (BCa) consists of breast-conserving surgery followed by several weeks of adjuvant breast radiotherapy (RT) and hormonal treatment. In an effort to improve convenience and quality of life for patients who receive breast irradiation, investigators have evaluated shorter, moderately hypofractionated whole-breast irradiation regimens[1–4]. Despite the improved convenience associated with such regimens, patients still require at least 3 weeks of daily treatment.

Most ipsilateral early BCa recurrences have been demonstrated to arise near the tumour bed[5,6]. Consequently, there is growing interest in partial-breast irradiation for early BCa as a means of effectively reducing local recurrence while obtaining the improved convenience of a shortened treatment schedule. Neoadjuvant single-fraction stereotactic RT (SBRT) is a novel form of partial-breast irradiation for early-stage BCa.

The purpose of the present study was to evaluate rates of pathologic response (pR) at the time of delayed surgery after neoadjuvant SBRT in our ongoing phase I trial (see NCT03917498 at https://ClinicalTrials.gov/).

METHODS

All postmenopausal women 65 years of age or older presenting with a new diagnosis of stage I (cT1N0), unifocal luminal A, estrogen receptor–positive, HER2-negative, grades 1–2 invasive BCa, whose planned surgery consisted of breast-conserving surgery with sentinel lymph node biopsy, were eligible for inclusion. The patients were

Correspondence to: Michael Yassa, Hôpital Maisonneuve-Rosemont, Department of Radiation Oncology, 5415 Boulevard de l'Assomption, Montreal, Quebec H1T 2M4. E-mail: myassa.hmr@ssss.gouv.qc.ca ■ **DOI:** https://doi.org/10.3747/co.27.6059

informed of their eligibility for this clinical trial by the surgical oncologist and, if interested, were referred to the radiation oncologist. Our institutional ethics board approved the trial, and informed consent was obtained from all participants.

Mammography and breast and axillary ultrasonography were used to confirm tumour stage. Any suspicious axillary lymph nodes were biopsied and histologically confirmed as disease-free before commencement of RT. The clip placed at the time of diagnostic biopsy was used to help with tumour localization.

Planning for RT consisted of immobilization using a breast board and VacLok device (Civco Medical Solutions, Orange City, IA, U.S.A.). Computed tomography simulation was performed in the supine position. The gross tumour volume was defined as the primary tumour based on physical exam, computed tomography, and breast ultrasonography. The clinical target volume included the gross tumour volume plus an additional 10 mm 3-dimensional expansion (cropped by 5 mm at the skin surface), excluding the chest wall and pectoralis major. The planning target volume consisted of a symmetrical 10 mm expansion around the clinical target volume. Critical structures included the thyroid gland, heart, lungs, skin, both breasts, and the ribs. An inverse-planning optimization technique was used to generate plans for a linear accelerator capable of delivering 20 Gy to the planning target volume in a single fraction while respecting target and critical structure dose–volume constraints (Table I). Before SBRT treatment delivery, cone-beam computed tomography confirmed patient positioning and target localization using the implanted marker as a surrogate.

Ipsilateral breast and axillary ultrasonography and a physical examination were performed 6 weeks after RT.

TABLE I Dosimetric constraints for normal structures

Structure	Dosimetric parameter	Per protocol	Endpoint (≥grade 3)
Heart			
Right breast Left breast	$D_{5\%}$	≤1 Gy ≤3 Gy	Pericarditis
Thyroid	$D_{100\%}$ D_{max}	≤0.6 Gy <3 Gy	Organ function
Skin	$D_{10\ cm3}$ D_{max}	≤20 Gy ≤21 Gy	Ulceration
Rib	$D_{1\ cm3}$ D_{max}	≤21 Gy ≤22 Gy	Pain or fracture
Ipsilateral lung	$D_{10\%}$ $D_{25\%}$	≤6 Gy ≤2 Gy	Pneumonitis
Ipsilateral breast	$V_{20\ Gy}$ $V_{10\ Gy}$	≤35% ≤60%	
Contralateral breast	D_{max}	≤3 Gy	

$D_{5\%/100\%/10\%/25\%}$ = dose covering 5%, 100%, 10%, or 25% of the volume respectively; D_{max} = maximal point dose; $D_{10\ cm3/1\ cm3}$ = maximal dose to a 10 cm^3 or 1 cm^3 volume respectively; $V_{20\ Gy/10\ Gy}$ = the percentage of the volume receiving a dose of 20 Gy or 10 Gy respectively.

Radiologic response was evaluated according to the Response Evaluation Criteria in Solid Tumors[7]. Any RT toxicity was assessed using the U.S. National Cancer Institute's *Common Terminology Criteria for Adverse Events*, and a nurse completed the European Organisation for Research and Treatment of Cancer's rating system for cosmetic results of breast-conserving treatment.

Surgery, consisting of a partial mastectomy guided by wire localization, with sentinel lymph node biopsy, was performed between weeks 11 and 13 after RT. Patients with positive margins after partial mastectomy underwent margin revision to achieve negative margins at ink.

A postoperative moderately hypofractionated whole-breast irradiation regimen was recommended for the following features: grade 3 tumour, lymphovascular invasion, tumour size 3 cm or larger, pT4 disease, triple-negative status, lobular histology, or extensive ductal carcinoma *in situ* (>25% tumour mass). Adjuvant postoperative chemotherapy therapy was given at the discretion of the treating surgical oncologist. All patients were offered postoperative endocrine therapy.

The trial aims to recruit a total of 20 patients. The primary endpoint is evaluation of pR as assessed by microscopic evaluation of the surgical specimen using the Miller–Payne system (a comparison of tumour cellularity in the biopsy and surgical specimens)[8]. The goal of the present interim analysis, halfway through recruitment, is to verify that the 3-month delay between RT and surgery does not lead to tumour progression. We also assessed immediate post-RT toxicity. Postoperative toxicities will be reported when the trial has reached at least 12 months of follow-up for all patients.

RESULTS

Between June 2018 and August 2019, 10 patients completed the planned treatment sequence. Median age of the patients was 72 years (range: 65–84 years). Median clinical tumour size on initial ultrasonography was 5.8 mm (range: 4 mm–14 mm). Six patients (60%) had grade 1 disease. All patients received RT as planned. No significant radiation complications were noted other than grade 1 dermatitis in the treated area.

No patient had tumour progression at the 6-week (post-RT) ultrasound. Median tumour size at the post-RT ultrasound was 5.9 mm (range: 4 mm–15 mm).

Surgery consisting of partial mastectomy guided by wire localization, with sentinel lymph node biopsy, was performed as planned in all 10 patients [average: 92 days (13.1 weeks)]. Median tumour bed size was 8 mm (range: 1.5 mm–17 mm) on pathology. Histologic analysis confirmed that 8 patients experienced a tumour pR to neoadjuvant RT. The pR was observed as a decrease in tumour cellularity. The corresponding Miller–Payne grade was 4/5 (>90% loss of tumour cells) in 4 patients, 3/5 (30%–90% loss of tumour cells) in 4 patients, and 1/5 (no response) in 2 patients. In the 8 patients experiencing a pR, median residual tumour cellularity was 3% (range: 1%–10%). No pathologic complete response was observed (Table II). All patients had negative sentinel nodes, except for 1 patient (patient 4) who had a microscopically positive sentinel node.

TABLE II Clinical and pathologic tumour information

Pt ID	Tumour grade	Tumour size on ultrasonography (cm)			Tumour cellular response (%)
		Before RT	6 Weeks after RT	At pathology	
1	1	0.4	0.45	0.9	0
2	1	0.55	0.57	0.6	0
3	1	0.9	0.9	0.6	99
4	2	1.4	1.5	1.7	95
5	1	0.6	0.6	0.15	99
6	2	0.5	0.26	0.15	99
7	1	0.51	0.4	0.8	99
8	2	1	0.9	0.9	95
9	1	0.7	0.58	0.8	90
10	2	0.5	0.6	0.8	99

Pt = patient; RT= radiotherapy.

DISCUSSION

In this pilot study, we present a novel treatment schedule for early-stage BCa. Standard therapy for this patient population involves breast-conserving surgery followed by several weeks of adjuvant RT. Neoadjuvant SBRT offers several theoretical advantages over standard adjuvant RT. First, the fact that the tumour is in place allows for easier target delineation and a smaller irradiated volume[9]. Also, tumour oxygenation might be improved, leading to an enhanced radiobiologic effect from neoadjuvant RT.

One of the first studies of preoperative partial-breast irradiation in early-stage BCa assessed the toxicity and cosmetic outcome of 40 Gy in 10 daily fractions, with surgery 6 weeks later[10]. In the 70-patient study cohort, RT-related and postoperative toxicities were low. Cosmetic outcome was good-to-excellent in 77% and 100% of patients at 6 and 12 months respectively. The pR rate was not reported. At a median follow-up of 23 months, 2 local recurrences had been detected.

Horton *et al.*[11] were the first to report on the use of single-fraction preoperative SBRT in a phase I dose-escalation study, but the interval between RT and surgery was relatively short. Those authors explored preoperative radiation at 3 dose escalation levels—15 Gy ($n = 8$), 18 Gy ($n = 8$), and 21 Gy ($n = 16$)—followed by surgery within 10 days for patients with early-stage unifocal BCa. At a median follow-up of 23 months, no acute dose-limiting grade 3 radiation-related toxicities or wound-healing problems were observed, and no patient experienced recurrence. No pR was reported.

On the other hand, Nichols *et al.*[12] used fractionated SBRT (38.5 Gy in 3.85 Gy fractions delivered twice daily), with surgery performed more than 21 days thereafter. Of 27 patients treated, 4 developed a complete pR by hematoxylin and eosin staining. With a little more than 3 years of follow-up, no failures were noted.

Interesting data from other trials are forthcoming. Our previous preliminary feasibility trial, which administered 20 Gy in a single fraction, with surgery immediately after RT (within 48–72 hours), is maturing (see NCT01717261 at https://ClinicalTrials.gov/). The primary outcome of that trial is acute toxicity, and secondary outcomes include ipsilateral BCa recurrence, chronic toxicity, and cosmesis. Other trials such as ABLATIVE are looking at longer intervals between RT and surgery. In the latter prospective single-arm study for women with early-stage BCa, preoperative RT will precede lumpectomy by 6 months[13].

There is also growing interest in the use of neoadjuvant RT as a means of avoiding surgery in other tumour sites as well. The use of SBRT as radical treatment has been extensively studied in non-small-cell lung cancer, with 2-year local control rates of approximately 90%[14]. A recent phase II study by Palma *et al.*[15] of lung SBRT set out to evaluate the pR rate with that treatment. When surgery was performed 10 weeks after SBRT, the pathologic complete response rate was 60% and the 2-year local control rate was 100%. Those results show that there might be a discrepancy between pR and long-term local control, and although purely speculative, the question is, might it be possible for a subset of patients with low-risk early-stage BCa to avoid surgery altogether?

CONCLUSIONS

Our trial demonstrates a safe method for delivering single-fraction RT with delayed surgery that, in most patients, can lead to high levels of pR as demonstrated by a significant decrease in tumour cellularity. To our knowledge, this report is the first describing tumour pR after single-fraction RT with delayed surgery for early BCa. Continued accrual to this study and subsequent trials are needed to determine the role and long-term safety of this novel technique in the management of early-stage BCa.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: PV has received honoraria from AbbVie, Sanofi, and TerSera Therapeutics. The remaining authors have no conflicts of interest to disclose.

AUTHOR AFFILIATIONS
*Department of Radiation Oncology, †Department of Pathology, and ‡Department of Surgery, Hôpital Maisonneuve-Rosemont, University of Montreal; §Department of Radiation Oncology, McGill University Health Centre, McGill University; and ‖Department of Radiology, Hôpital Maisonneuve-Rosemont, University of Montreal, Montreal, QC.

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