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Original Article

Single pre-operative radiation therapy (SPORT-CK) trial for low-risk breast cancer: Early results of a phase 2 study

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ABSTRACT

Background and purpose: Preoperative partial breast irradiation (PBI) is a novel technique that can be used in patients with early-stage breast cancer with the goal of limiting the irradiated breast volume, toxicity and number of fractions. The aim of this trial is to assess the toxicity, surgical, oncologic and cosmetic outcomes of preoperative PBI.

Materials and Methods: In this single-arm phase II trial, we enrolled women ≥ 60 years, with unifocal low-risk breast invasive ductal carcinoma (cT1N0, grade 1–2, ER+, Her2-). Patients were treated with a single fraction of 20 Gy of preoperative PBI using volumetric modulated arc therapy (VMAT). Patients then underwent breast-conserving surgery (BCS) +/- sentinel lymph node biopsy within 72 h of radiation. Primary outcomes were rate of surgical complications and early toxicity. Secondary outcomes were cosmesis at 12 months, chronic toxicity and ipsilateral breast tumor recurrence.

Results: Twenty-five patients were recruited with a median age of 67 years, and a median follow-up of 60 months. Sentinel biopsy was positive in 1 out of 24 patients (4 %). Two patients received adjuvant RT for close margins or positive lymph nodes. Within the first 90 days, none of the patients had surgical complications; almost all had grade 0 to 1 acute and late RTOG skin toxicity. The cosmetic outcome was rated between good and excellent in all cases by physicians and patients, except for one patient who self-rated her cosmesis as fair as of the third year. There were no recurrences.

Conclusion: Preoperative single-fraction PBI is a safe and feasible treatment for elderly patients with low-risk early-stage breast cancer, with no surgical complications, very low rates of acute and late radiation toxicity, and excellent cosmetic outcomes. Randomized controlled trials are needed to compare preoperative to adjuvant PBI in this patient population.

Introduction

Adjuvant whole breast radiation therapy (WBRT) following breast-conserving surgery (BCS) in early-stage breast cancer has been shown to improve survival as compared to total mastectomy [1]. Treatment consisting of 5 to 16 fractions, using external beam radiation therapy, to the whole or partial breast, is currently the standard of care [2–4].

Despite the effectiveness of adjuvant radiation therapy and the implementation of hypofractionation, many patients undergo total mastectomy for early-stage breast cancer to omit radiation therapy due

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to the relatively long treatment schedule and distance to radiation centers, particularly for individuals residing in rural areas [5–6].

Recently, the implementation of accelerated external beam partial breast irradiation (PBI), intraoperative irradiation and brachytherapy, in selected cases of early-stage breast cancer patients, has led to reduced overall treatment duration, improved cosmetic outcomes, enhanced patient adherence, while maintaining the same oncologic outcomes, when compared to traditional radiation therapy schedules [7–10].

Treating with partial breast irradiation post-operatively poses a significant challenge due to the complexity of accurately delineating the lumpectomy cavity, particularly following oncoplastic breast-conserving surgeries, and often resulting in larger treated volumes [11]. Therefore, the role of preoperative RT has been recently emphasized, with the main advantage of treating a well-delineated volume, decreasing the dose to the intact breast tissue, and the possibility of decreasing the size of the lesion, enabling more conservative surgeries [12].

Brachytherapy and intraoperative RT such as Intrabeam®, delivering a high dose to the surgical cavity, have shown excellent long-term local control, survival, and cosmesis [9–10], but require special equipment and extensive training, making them less suitable for widespread implementation. Preoperative radiation therapy, using the widely available volumetric modulated arc therapy technique (VMAT), could achieve similar oncologic and cosmetic results.

While the specific findings and recommendations may vary for different types of cancers and radiation protocols, the principle of timing surgery to leverage the beneficial acute effects of radiation on tissue response and wound healing applies broadly. Based on the findings from studies on short-course radiotherapy for rectal cancers, it appears that reducing the interval between radiotherapy and surgery lowers the likelihood of experiencing immediate surgical complications. This effect is primarily attributed to an enhanced leukocyte response occurring beyond three days post-radiotherapy [13–16]. Therefore, we decided to operate within the first 72 h after radiation therapy to mitigate the expected increased risk of side effects from the high-dose treatment that could escalate with time. Additionally, in the preoperative setting, the region receiving the highest radiation dose is often completely excised during the segmental mastectomy, reducing the risk of fibrosis or necrosis in the treated breast tissue and potentially enhancing cosmetic outcomes [17].

In that context, we designed a phase 2 trial using a single high-dose fraction of 20 Gy delivered with VMAT in carefully selected patients with favorable, early-stage breast cancers, within 72 h of segmental mastectomy. In this trial, we assessed the feasibility, acute and late toxicity, disease control, and cosmetic outcomes.

Materials and Methods

Study design and participants

The SPORT-CK trial is a prospective phase 2 trial conducted in a tertiary centre. Female patients aged 60 years or older, diagnosed with a unifocal stage I (cT1-2 N0), ER positive, HER2 negative, grade 1–2 invasive ductal carcinoma were eligible for the study. Breast imaging, consisting of mammography, breast MRI and/or breast and axillary ultrasound (US), along with a biopsy of the tumor with fiducials placement, performed up to 12 weeks before treatment were required. Suspicious axillary lymph nodes were biopsied and confirmed as free of disease. Adjuvant systemic treatment was initiated as per the institutional protocol. The main exclusion criteria included a known deleterious mutation in BRCA1 and/or BRCA2 genes, exclusive ductal carcinoma in situ or lobular carcinoma histology, lymphovascular invasion, preoperative hormonal therapy or chemotherapy, prior history of cancer, and serious comorbidities precluding definitive RT or surgery. The study was conducted according to the Declaration of Helsinki and approved by the institutional ethical review board. All patients provided written informed consent.

Treatment and trial procedures

Patients were immobilized using a breast board and VacLok device in supine position. CT simulation was done with slices thickness of ≤ 3 mm. Gross tumor volume (GTV) was delineated on the planning CT using the fiducials, and taking into consideration the mammograms, MRI and US images, as well as all clinical information. Clinical target volume (CTV) was constructed by adding a 5–10 mm expansion to GTV; thoracic wall and pectoral muscles were excluded from CTV as well as 5 mm from the skin surface. Planning target volume (PTV) consisted of a symmetrical 7–10 mm expansion around the CTV. Planning target evaluated volume (PTV_EVAL) consisted of the PTV cropped to the chest wall (consisting of the ribs and intercostal muscles) and the pectoralis muscles, as well as 5 mm from the skin surface. Part of the chest wall and intercostal muscles were included in the PTV_EVAL if clinically warranted. 20 Gy in a single fraction were prescribed such as 95 % of the prescribed dose covered 95 % of the PTV_EVAL. Critical structures included the heart, lungs, skin, breasts, thyroid gland, and the ribs. Volumetric modulated arc therapy (VMAT) plans were generated using an inverse-planning optimization technique while respecting target and critical structure dose-volume constraints (Supplementary Table 1).

Patients underwent breast-conserving surgery with sentinel lymph node biopsy (SNLB) within 72 h of RT. For patients above the age of 70, SLNB was optional. Margin revision was performed if the margins were positive.

Table 1
Patient and tumor characteristics.

Variable	*(n = 25)*
Age, years (median, range)	67 (60–81)
Follow-up length, months (median, range)	60 (24–89)
Laterality (number, %)	
Right	13 (52)
Left	12 (48)
Clinical size, mm (mean, range)	10.2 (3.4–18)
Pathologic size, mm (mean, range)	12 (6–20)
Grade (number, %)	
Grade 1	15 (60)
Grade 2	10 (40)
Estrogen Receptor (number, %)	
Positive	25 (100)
Negative	0 (0)
Progesterone Receptor (number, %)	
Positive	23 (92)
Negative	2 (8)
Lympho-vascular Invasion	
Negative	17 (68)
Unknown	8 (32)
Ductal carcinoma in situ	
Present	16 (64)
Absent	9 (36)
Sentinel Lymph node biopsyNumber of nodes removed (median, range)	2 (0–5)
Negative (n, %)	23 (92)
Positive (n, %)	1 (4)
Not available (n, %)	1 (4)
Initial surgical margins (number, %)	
Negative	19(76)
Close for DCIS<1mm	4(16)
Positive for invasive carcinoma	1(4)
Positive for DCIS	1(4)
Surgical margin revision (number, %)	5(20)
Adjuvant RT (number, %)	
Whole breast	1(4)
Loco-regional	1(4)
Adjuvant systemic therapy (number, %)	
Endocrine therapy alone	23 (92)
Chemotherapy alone	0 (0)
Endocrine and chemotherapy	2 (8)

Abbreviations: n = number of patients; DCIS: ductal carcinoma in situ.

If high-risk features were found on surgical pathology (these features include tumors > 3 cm, grade 3, positive SLNB or close final margin < 1 mm for either DCIS or invasive component where re-excision surgery was not performed), postoperative moderately hypofractionated RT was delivered.

Follow-up

Patients were assessed prior to treatment, on postoperative days 7 and 14, and then 3, 6 and 12 months post-RT for the first year and then annually for 10 years along with annual mammograms.

Follow-up included history and physical examination, EORTC Breast Cancer Cosmetic Rating and RTOG/EORTC Late Radiation Toxicity Scale questionnaires, NCI CTCAE Common Toxicity Scales as well as bilateral breast digital photographs.

Statistical analyses

Descriptive statistics were produced concerning patient and tumor characteristics, acute and chronic toxicities, and cosmetic results. Recurrence rates were analyzed by the Kaplan-Meier curves, time to recurrence being defined as the time between surgery and failure.

Results

Twenty-five patients were enrolled in the trial between October 2016 and July 2022 in one centre in Montreal, Canada and underwent pre-operative RT, 20 Gy in 1 fraction, prior to breast conserving surgery. All patients underwent preoperative RT and surgery within 72 h, without any delay. SLNB was omitted in one patient aged 75 and with tubular carcinoma, who subsequently did not receive postoperative RT. Two patients had positive margins and 4 patients had close margins of DCIS<1mm; 5 of those six underwent margin revision. The sixth patient, with close margins, received postoperative WBRT, 42.56 Gy in 16 fractions.

Another patient received loco-regional RT, 42.56 Gy in 16 fractions to the breast and 40.05 Gy to the axilla and supraclavicular area, due to a positive sentinel lymph node.

Only one patient had LVI on final pathology, with a negative SLNB, and she did not receive adjuvant RT. All patients initiated adjuvant endocrine therapy, while two patients also received adjuvant chemotherapy, because of positive nodes and an elevated Oncotype Dx score. The patients and tumor characteristics are summarized in Table 1. The dosimetric characteristics of the plans are presented in Table 2.

None of the patients had surgical complications such as scar healing delay, surgical site infections or hematomas within the first 90 days. Most patients had grade 0 to 1 RTOG/EORTC early radiation toxicity (Fig. 1). Two patients reported grade 2 breast pain on days 2 and 7, that improved afterwards; one patient reported grade 2 dermatitis at 3 months. With regards to the RTOG/EORTC late radiation toxicity to skin and subcutaneous tissues, only one patient had grade 2 skin atrophy at 4 years. Four patients had grade 2 subcutaneous skin fibrosis grade 2 at different time points (two at 6 months, one at 1 year and one at 2 years). In these 4 cases, the fibrosis was rated as grade 0–1 on further follow-ups (Fig. 2). None of the patients had grade 3 acute or late toxicity.

The overall cosmesis was rated by patients and physicians simultaneously at each visit (Fig. 3). The ratings were all satisfactory (good to excellent), whereas one patient self-rated her cosmesis as fair at years 3, 4 and 5.

None of the study patients developed pericarditis, pneumonitis, fat necrosis or chronic mastitis.

At median follow-up of 60 months, none of the patients developed local, regional or distant recurrences. Two patients passed away, 26 and 39 months after treatment, due to unrelated abdominal pathology and lung cancer developed one year after surgery, respectively. No breast cancer related deaths were reported.

Table 2
Dosimetry of treated patients (n = 25).

Variable	Mean	Range
Treated volumes, cc		
GTV	1.3	0.1–3.8
CTV	10.6	2.3–60.2
PTV	44.7	15.4–110
PTV_EVAL	39.8	12.8–104.3
PTV to breast volume ratio, %	5.27	1.4–14.3
Total margin from GTV to PTV, cm	1.6	1.3–2.1
Maximum dose, Gy	21.1	20.4–22.0
Mean Lung dose, Gy		
Ipsilateral breast	0.64	0.17–1.1
Contralateral breast	0.11	0.05–0.2
Mean Heart dose, Gy		
Right-sided cancer	0.22	0–0.6
Left-sided cancer	0.22	0–0.3
Ribs dose, Gy		
Dmax	10.9	2.1–18.4
D1cc	7.85	1.8–13.8
Skin dose, Gy		
Dmax	17.5	10–20
D10cc	7	1.9–11.9

Abbreviations: n = number of patients; GTV=Gross tumour volume; CTV=Clinical target volume; PTV=Planning target volume; PTV_EVAL=Evaluated PTV; Dmax = maximal dose; D10cc = Dose to 10 cc of a structure; D1cc = Dose to a volume of 1 cc of a structure.

Discussion

Recent advances in radiation oncology have allowed a rapid transition towards precision medicine approaches. Preoperative accelerated PBI represents a change toward an effective de-escalation of treatment in selected cases of early-stage breast cancer.

Preoperative RT for breast cancer is still an emerging modality of treatment of breast cancer, since it requires a change of procedures, with the multidisciplinary involvement of radiation oncologists very early after diagnosis. To allow for broader applicability of the results of this trial, we used a VMAT technique that can be replicated in most radiation oncology departments and that delivers highly conformal plans that spare the normal breast tissue.

The early results of this trial show that patients treated with a single fraction of 20 Gy preoperatively experienced mild adverse effects, with no acute toxicity cases exceeding grade 2. 2 patients had grade 2 breast pain on day 7 and 14, but we note that these are common side effects after BCS.

All patients were operated within the 72-hour window post-RT, and none had acute surgical complications such as wound dehiscence or healing delay.

This contrasts with our own experience with Intrabeam® RT, where 61 patients with early-stage breast cancer received 20 Gy in a single fraction. Patients with high-risk features on pathology received adjuvant whole breast RT. With a median follow-up of 3.9 years, none of the patients experienced loco-regional relapses. However, the incidence of surgical complications (such as seroma, hematoma, cellulitis, and fat necrosis) and grade 3 RT toxicity was higher compared to the SPORT-CK outcomes. Specifically, the rate of seroma collection was 17.5 % in patients receiving Intrabeam® only versus 33.3 % in patients receiving both modalities, while fat necrosis, it was 2.5 % and 4.8 %, respectively. Additionally, two patients experienced grade 3 skin reactions Martinez et al., 2023 Sep 1 [cited 2024 Jul 20];8 [18]..

Our study resembles the recently published ROCK trial conducted by Meattini et al. [19] where 22 patients with early stage breast cancer received preoperative RT using Cyberknife® with a dose of 21 Gy in a single fraction 2 weeks prior to surgery, with a follow-up to 18 months. The rate of acute toxicity was low, similar to our trial, where none of the patients had more than grade 2 toxicities, and only one patient has grade 2 breast edema at day 7 and day 30. Like our trial, none of the patients

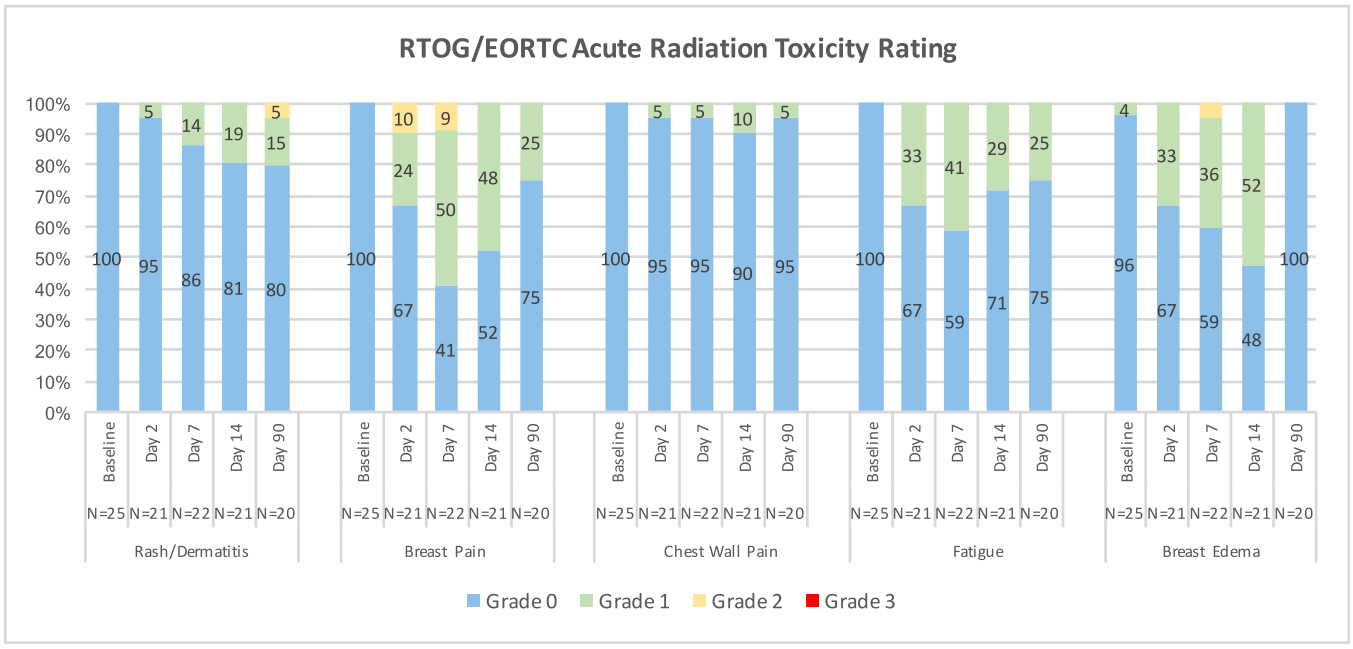

Fig. 1. RTOG/EORTC acute radiation toxicity rating for 5 domains, prior to treatment, and at days 2, 7, 14 and 90. N represents the number of patients assessed at a given timepoint, while the numbers in the columns represent the percentage of patients for a given rating.

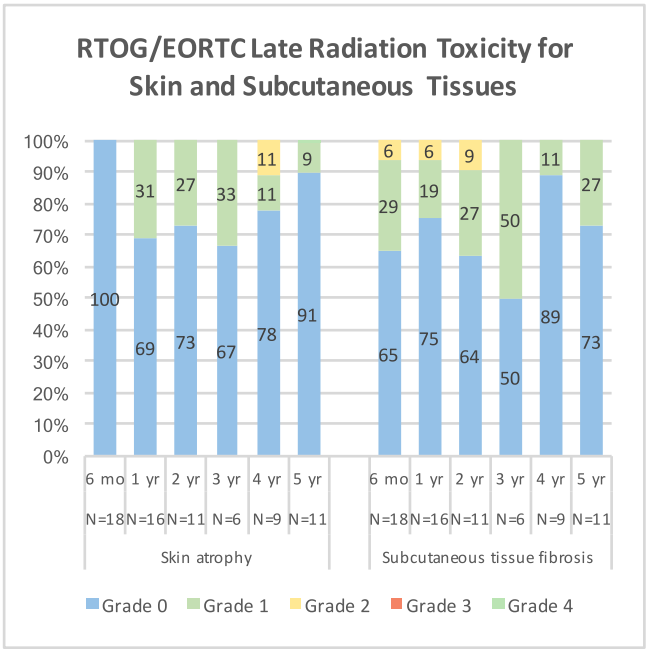

Fig. 2. RTOG/EORTC late radiation toxicity rating for skin and subcutaneous tissue at 6 months, and years 1 to 5. N represents the number of patients assessed at a given timepoint, while the numbers in the columns represent the percentage of patients for a given rating.

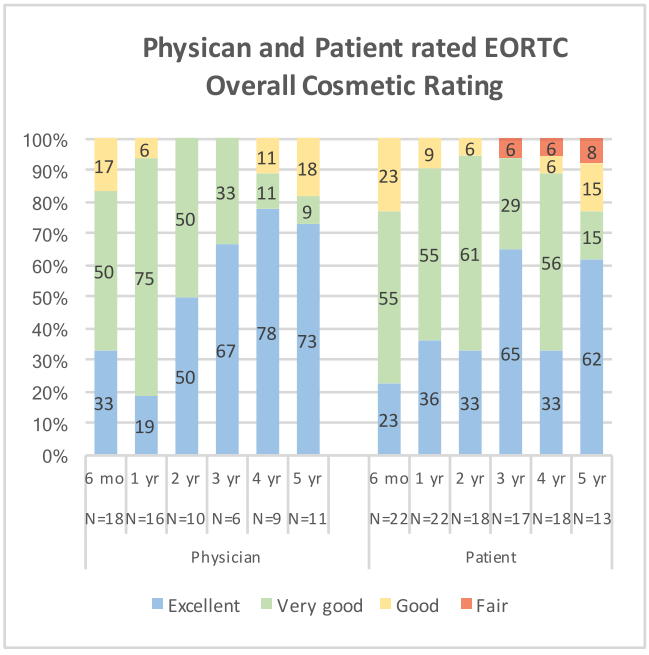

Fig. 3. Physician and patient rated EORTC overall cosmetic rating at 6 months, and at years 1 to 5. N represents the number of patients assessed at a given time point, while the numbers in the columns represent the percentage of patients for a given rating.

developed surgical complications. The cosmetic outcome was assessed by physicians every 3 months for the first year. At one year, 76.2 % (n = 16) had good to excellent outcomes, compared to three fair (14.3 %) and two (9.5 %) poor outcomes. In our trial, the one-year cosmesis was better, where 94 % (n = 15) of the cases had very good to excellent outcomes, and only one (6 %) had a good result. The difference could be attributed to the higher dose used in the ROCK trial, or the timing of the surgery. In fact, considering an α/β of 3 for normal tissues of the breast, the 20 and 21 Gy single doses are equivalent to a 92 and 101 Gy dose in 2-Gy fractions, respectively (EQD2). The variation in timing of surgery (two weeks in ROCK study, compared to 3 days in our study) could potentially affect RT-induced connective tissue remodeling and the inflammatory response's impact on postoperative wound healing. Identifying the optimal timing for surgery remains challenging, underscoring the need for future clinical trials to establish an optimal workflow that maximizes the therapeutic benefits.

Moreover, the SIGNAL trial utilized preoperative SBRT with a single dose of 21 Gy, followed by BCS within 7 days, and demonstrated no

surgical complications, which aligns with our findings. Ninety-two percent of the patients achieved good to excellent cosmetic outcomes as assessed by physicians. The brief interval between RT and BCS may have contributed to the improved cosmesis [20].

Our results also compare well with another study by Horton et al. where preoperative RT was delivered using three different doses of 5, 18 and 21 Gy and showed no grade 3 acute or late toxicities among the different doses used. All patients had good to excellent cosmetic outcomes and none had recurrences at a mean follow-up of 23 months [21]. In our study, we used a dose of 20 Gy since doses of 18 Gy and 21 Gy have been shown to be safe and effective. Only one patient developed grade 2 fibrosis at 2 and 3 years (14.2 % and 20 % respectively). The percentage is higher than other studies due to the small number of patients on follow-up beyond 2 years (7 and 5 patients respectively).

In the phase II PAPBI trial published by Bosma et al. in 2020, where preoperative PBI was delivered using 2 different schedules of 4 Gy x 10 fractions or 6 Gy x 5 fractions, 6 weeks before surgery, the rate of postoperative complications was 14 %. 10 % of patients had a at least moderate fibrosis at 2 years, with improved cosmesis at 5 years [22].

Mulliez et al. published in 2022 the results of their 5-fraction preoperative WBRT using a dose of 25 Gy to the breast with simultaneous integrated boost of 30 Gy to the lesion, delivered 4 to 8 weeks before the surgery. 5 of the 14 patients had wound problems such as mastitis and fistulas [23]. This correlates with other tumor sites such as sarcoma where preoperative radiation is associated with increased risk of healing delays. In this trial, the surgery was done within 3 days to prevent surgical complications, and it is the first study to deliver RT as early as a few hours before surgery.

The short interval between RT and surgery did not allow for a radiation treatment effect, or disease downstaging, and was chosen to reduce the risk of treatment complications. A waiting time of at least 6 weeks is needed to evaluate the chances of complete pathologic responses [12,24–26].

This novel approach to treating early-stage breast cancer with a single fraction of radiation therapy (RT) has reduced the overall treatment duration compared to the traditional postoperative regimen spanning one to three weeks, which typically begins no sooner than three weeks after surgery. The single fraction treatment is more convenient and accessible for patients residing far from radiation oncology centers. It also has the potential of improving compliance and enhancing quality of life, particularly for elderly patients. This streamlined approach allows patients to undergo both RT and breast-conserving surgery (BCS) within 24–48 h, thereby reducing hospital visits.

To date, none of the patients had recurrences, in the context of adjuvant endocrine therapy and a short follow-up. A longer follow-up and larger trials are needed since the rate of recurrences is very low in this low-risk patient population, with recurrences usually occurring at several years after local treatment.

In this context, a key question is whether this patient population truly requires radiation therapy. Multiple trials in which patients received endocrine therapy while omitting RT have shown acceptable local control rates, although recurrences were higher when RT was omitted [27–29]. This then brings the question of whether RT alone instead of endocrine therapy might be an appropriate treatment in this patient population. The ongoing randomized Europa trial will randomize patients to postoperative radiation therapy alone versus hormonal therapy only and will assess if radiation therapy may help avoid the long-term toxicity of endocrine therapy and could potentially improve quality of life in this population [30]. If the Europa trial is positive, treatments like the one given in the SPORT-CK trial might then become even more worthwhile: patients receive all oncologic treatments (preoperative RT and surgery) in the span of 72 h, in a one-stop fashion.

There is a recent rising interest in identifying a subset of patients exhibiting a higher probability of achieving a pathological complete response (pCR) to RT, in order to undergo a "wait and see" approach instead of surgery. One of the ongoing trials is led by our research group. It is a phase 2 trial entitled "Single PreOperative Radiation Therapy with Delayed or No Surgery (SPORT-DNS)" that includes women of 50 and above, with ER+early-stage breast cancer with Oncotype DX≤18 where patients will be treated with the same dose of 20 Gy in single fraction.

Patient will be followed for 12 months, and if they are 70 years of age or above, with complete clinical response to treatment, surgery may be omitted until recurrence.

Conclusion

This trial showed that preoperative PBI delivered in a single fraction of 20 Gy using external beam techniques is a novel, feasible and well-tolerated regimen for selected cases of early-stage breast cancer. Initial tumor control rates, acute and late toxicity, as well as cosmetic outcome are excellent. Longer follow-up is needed to assess late side effects and tumor control. Large phase 3 studies comparing preoperative to postoperative radiation are needed.

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CRediT authorship contribution statement

Dima Mahmoud: Writing – original draft, Visualization, Supervision, Software, Resources, Formal analysis, Data curation. **Michael Yassa:** . **Leticia Alvarado:** Writing – review & editing, Resources, Investigation, Formal analysis. **Christine Lambert:** Writing – review & editing, Resources, Methodology, Investigation, Conceptualization. **Sarkis Meterissian:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Dawn Anderson:** Writing – review & editing, Validation, Resources, Investigation, Formal analysis, Conceptualization. **Francine Tremblay:** Writing – review & editing, Supervision, Resources, Investigation, Conceptualization. **Naim Otaky:** Writing – review & editing, Visualization, Resources, Investigation, Conceptualization. **John Keyserlingk:** Writing – review & editing, Validation, Resources, Investigation, Conceptualization. **Valerie Panet-Raymond:** Validation, Resources, Methodology, Formal analysis, Conceptualization. **Neil Kopek:** Writing – review & editing, Validation, Resources, Methodology, Conceptualization. **Marc David:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Marie Duclos:** Writing – review & editing, Visualization, Resources, Conceptualization. **Catherine Pembroke:** Investigation, Data curation. **David Fleiszer:** Writing – review & editing, Visualization, Resources, Methodology, Conceptualization. **Ari N Meguerditchian:** Writing – review & editing, Validation, Resources, Conceptualization. **Antoine Loutfi:** Writing – review & editing, Validation, Resources, Investigation, Conceptualization. **Danny Lavigne:** Writing – review & editing, Visualization, Supervision, Investigation, Conceptualization. **Tarek Hijal:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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