

Choosing wisely after publication of level I evidence in breast cancer radiotherapy

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Background: Recent trials in early-stage breast cancer support hypofractionated whole-breast radiotherapy (WBRT) as part of breast-conserving therapy (BCT). Evidence also suggests that radiotherapy (RT) omission may be reasonable for some patients over 70 years. Among radiation-delivery techniques, intensity-modulated RT (IMRT) is more expensive than 3-dimensional conformal RT (3DCRT). Based on this evidence, in 2013, the American Society for Radiation Oncology (ASTRO) recommended hypofractionated schedules for women aged ≥ 50 years with early-stage breast cancer and avoiding routine use of IMRT for WBRT. To assess response to level I evidence and adherence to ASTRO recommendations, we evaluated the pattern of RT use for early-stage breast cancer at our National Comprehensive Cancer Network institution from 2006 to 2008 and 2011 to 2013 and compared the results with national trends.

Methods: Data from a prospective database were extracted to include patients treated with BCT, aged ≥ 50 years, with histologic findings of invasive ductal carcinoma, stage T1-T2N0M0, estrogen receptor-positive, and HER2 normal. We retrospectively reviewed the medical records and estimated costs based on 2016 Hospital Outpatient Prospective Payment System (technical fees) and Medicare Physician Fee Schedule (professional fees).

Results: Among 55 cases from 2006 to 2008, treatment regimens were 11% hypofractionated, 69% traditional schedule, and 20% RT omission (29% of patients were aged >70 years). Among 83 cases from 2011 to 2013, treatment regimens were 54% hypofractionated, 19% traditional schedule, and 27% RT omission (48% of patients were aged >70 years). 3DCRT was used for all WBRT treatments. Direct medical cost estimates were as follows: 15 fractions 3DCRT, \$7,197.87; 15 fractions IMRT, \$11,232.33; 25 fractions 3DCRT, \$9,731.39; and 25 fractions IMRT, \$16,877.45.

Conclusion: Despite apparent resistance to shorter radiation schedules in the United States, we demonstrate that rapid practice change in response to level I evidence is feasible. Wider adoption of evidence-based guidelines in early-stage breast cancer may substantially lower health care costs and improve convenience for patients without sacrificing oncologic outcomes.

Keywords: breast cancer, CALGB, choosing wisely, hypofractionation, omission, UK START

Plain language summary

Breast-conserving therapy allows many women with breast cancer to avoid mastectomy. After surgery, women have typically received at least 5 weeks of daily radiation to the whole breast. However, recent studies have shown that 3 weeks of daily radiation to the whole breast or even no radiation at all are options for some women. In addition, expensive radiation-delivery techniques may not be necessary for most whole-breast radiation. Whole breast radiation practice patterns in the US have been slow to change. For appropriately selected patients, we evaluated our

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practice patterns with regard to shorter radiation schedules, omission of whole-breast radiation, and use of different radiation-delivery techniques. We showed rapid practice change favoring shorter radiation schedules and omission of whole-breast radiation. Estimated cost savings by using shorter radiation schedules with appropriate radiation-delivery techniques may be substantial. Importantly, by adopting these practice changes, women with breast cancer are spared weeks of potentially unnecessary treatment.

Introduction

Adjuvant whole-breast radiotherapy (WBRT) plays an integral role in breast-conserving therapy (BCT) for women with early-stage breast cancer. In the landmark National Surgical Adjuvant Breast and Bowel Project¹ and Milan² trials, WBRT consisted of 50.0 Gy delivered in 25 daily fractions. However, patient inconvenience caused by 5 weeks of WBRT, increasing cost with each additional fraction, and limited resources led to interest in a shorter regimen. From a radiobiologic perspective, a shorter schedule delivering a higher daily dose of radiation over fewer treatment days (hypofractionated) can be equally effective.³ Concerns regarding long-term cosmetic results with a higher daily dose were allayed by 2 randomized trials in Canada and the United Kingdom.^{4,5} The hypofractionated schedules used in these trials thus seemed safe and would reduce the number of days required of patients while at the same time reducing resource utilization.

Three major randomized trials in Canada and the United Kingdom have now assessed traditional (50.0 Gy given in 25 fractions) versus hypofractionated WBRT for early-stage breast cancer.⁶⁻⁸ The Ontario Clinical Oncology Group (OCOG) compared traditional versus hypofractionated WBRT (42.5 Gy given in 16 fractions) after breast conservation surgery for early-stage breast cancer. At 10-year follow-up, Whelan et al⁶ reported no difference between the two fractionation schedules with regard to adverse effects, cosmetic outcome, local recurrence, or overall survival. The UK Standardisation of Breast Radiotherapy (START) Trialists' Group randomized women with early-stage breast cancer treated with primary surgery to either traditional WBRT or one of two hypofractionated schedules (41.6 Gy in 13 fractions or 39.0 Gy in 13 fractions).⁷ At 5-year follow-up, they found no difference in local recurrence and fewer adverse effects in the 39.0 Gy arm. The START Trialists' Group also performed START B, which randomized women with early-stage breast cancer to traditional versus hypofractionated WBRT (40.0 Gy in 15 fractions) after primary surgery.⁸ At 6-year follow-up, they found no difference in local recurrence. However, women in the hypofractionated arm had

reduced late adverse effects, fewer distant metastases, greater disease-free survival, and greater overall survival. The benefits of the hypofractionated schedules in the START A and B trials were maintained at 10-year follow-up.⁹

In 2009, the National Institute for Health and Clinical Excellence in the United Kingdom recommended hypofractionated WBRT as standard of care for early-stage breast cancer. Most patients in the United Kingdom are now treated with hypofractionated schedules.¹⁰ Subsequently, the American Society for Radiation Oncology (ASTRO) issued an evidence-based guideline regarding fractionation for whole-breast irradiation. The ASTRO evidence-based guideline supports the use of hypofractionated WBRT for patients aged ≥ 50 years, stage pT1-T2 pN0M0, with no prior chemotherapy, as long as the hypofractionated radiation plan can achieve radiation dose heterogeneity of $\leq 7\%$.¹¹

Although WBRT reduces the local recurrence rate for all breast cancers after breast-conserving surgery, the absolute benefit is quite small for elderly women. In the Cancer and Leukemia Group B (CALGB) 9343 study, women aged ≥ 70 years with estrogen receptor-positive (ER+) early-stage breast cancer were randomized to lumpectomy plus tamoxifen with or without WBRT.¹² At 10-year follow-up, CALGB 9343 showed a small improvement in local recurrence (10% vs 2%) and no difference in breast preservation, distant metastasis, and overall survival.¹² National Comprehensive Center Network (NCCN) guidelines now reflect these data, offering radiotherapy (RT) omission as an option for elderly women with hormone receptor-positive, early-stage breast cancer.¹³

In terms of treatment technique for delivery of WBRT, 3-dimensional conformal RT (3DCRT) or intensity-modulated RT (IMRT) are most common. The last cost comparison reported in the literature showed that a course of WBRT using IMRT was roughly twice the cost of 3DCRT. However, this information has now become outdated, as it was assessed using the 2003 Medicare fee schedule.¹⁴ One randomized trial reported clinically greater breast induration and change in breast appearance favoring IMRT versus 2-dimensional RT (2DRT), with no difference in quality of life.¹⁵ Randomized comparisons between IMRT and modern 3DCRT are lacking; however, one randomized trial compared IMRT with 2DRT, with computed tomography imaging used for planning in both arms.¹⁶ Reduced moist desquamation was associated with IMRT and smaller breast size. However, no difference in pain or quality of life was noted for IMRT versus 2DRT.¹⁶ Long-term follow-up showed no difference in chronic pain, quality of life, or cosmesis between IMRT

and 2DRT.¹⁷ In the absence of clear clinical benefit, routine IMRT use for WBRT remains controversial.

On the basis of updated level I evidence, ASTRO released practice recommendations in 2013 as part of the national Choosing Wisely campaign.¹⁸ For breast cancer, clinicians are encouraged to 1) consider shorter treatment schedules for women aged ≥ 50 years with early-stage breast cancer and 2) not routinely use IMRT to deliver WBRT.

To assess how practice patterns changed following the publication of level I evidence supporting hypofractionated WBRT,^{6–8} we evaluated the pattern of use of RT for women aged ≥ 50 years with hormone receptor-positive, early-stage breast cancer at our NCCN member institution.

Methods

Two time periods were evaluated, 2006 through 2008 and 2011 through 2013, defined by date of lumpectomy. The time periods were selected to assess 3 years before and 3 years after publication of the START trials and the long-term follow-up of the OCOG trial.

Patients were identified from a prospective breast cancer database which along with this study, was approved by the Mayo Clinic Institutional Review Board, and written informed consent was obtained from all participants for the use of the data for research purposes. Inclusion criteria were completion of BCT at our institution, age ≥ 50 years, histologic findings of invasive ductal carcinoma, stage T1-T2N0M0, ER+, and HER2 normal. These inclusion criteria were chosen to match the ASTRO recommended guidelines for shorter whole-breast radiation schedules.¹⁸ Patients receiving brachytherapy on clinical trial were excluded. We collected additional data from our institutional electronic medical record. Cases were categorized by RT modality (3DCRT, IMRT) and fractionation schedule (traditional >23 fractions vs hypofractionated <17 fractions, excluding boost).

Continuous variables were compared using the *t* test. Categorical variables were compared using the chi-squared test. A *P* value <0.05 was considered statistically significant. Cases were analyzed on an intent-to-treat basis.

Direct medical costs were estimated for 15- and 25-fraction WBRT using 3DCRT or IMRT, based on the Current Procedural Terminology, Fourth Edition, coding system. Payment rates are national average payments under the 2016 Hospital Outpatient Prospective Payment System (technical fees) and Medicare Physician Fee Schedule (professional fees).^{19,20}

Results

From 2006 to 2008, 55 patients met the inclusion criteria (mean [SD] age, 72.1 [9.0] years; range 51–89 years). WBRT

was given on a traditional schedule for 69% of patients and was hypofractionated for 11%. RT was omitted in 20% of all patients (mean [SD] age, 80.6 [6.3] years; range, 67–89 years). For patients aged >70 years, RT was omitted in 29%.

From 2011 to 2013, 83 patients met the inclusion criteria (mean [SD] age, 70.7 [8.9] years; range, 51–97 years). WBRT was given on a traditional schedule for 19% of patients and was hypofractionated for 54%. RT was omitted for 27% of all patients (mean [SD] age, 78.5 [7.6] years; range, 61–97 years). For patients aged >70 years, RT was omitted in 48%.

Between the two time periods, no significant differences were seen in patient age ($P=0.37$), proportion of patients aged >70 years ($P=0.22$), or disease stage ($P=0.95$). The change in radiation therapy practice patterns between the two time periods was statistically significant ($P<0.001$) (Table 1). When only WBRT patients were considered, the hypofractionation rate increased from 14% in 2006–2008 to 74% in 2011–2013 ($P<0.001$) (Figure 1). For patients aged >70 years, the RT omission rate increased from 29% in 2006–2008 to 48% in 2011–2013; however, it did not reach statistical significance ($P=0.11$) (Table 1; Figure 1).

The rationale for the treatment using a traditional rather than a hypofractionated schedule was documented in medical records in 11 of 16 traditional schedule cases from 2011 to 2013. In six cases, patient preference led to using the traditional schedule. In five cases, the treating physician recommended a traditional schedule because of a large breast separation. Of the five remaining cases in which the rationale for choosing a traditional schedule was not clear, one patient had breast implants and two patients were initially planned

Table 1 RT practice patterns for patients aged ≥ 50 years with hormone receptor-positive, early-stage breast cancer at our NCCN-member institution

Characteristic	Years		P-value
	2006–2008	2011–2013	
Patients (N)	55	83	
Age (SD), mean, years	72.1 (9.0)	70.7 (8.9)	0.37
Stage			
T1a	5	8	0.95
T1b	21	29	–
T1c	24	36	–
T2	5	10	–
RT practice patterns, N (%)			
Traditional WBRT	38 (69.1)	16 (19.3)	<0.001
Hypofractionated WBRT	6 (10.9)	45 (54.2)	–
RT omission	11 (20.0)	22 (26.5)	–
Age >70 years, N	34	42	0.22
RT omission, N (%)	10 (29.4)	20 (47.6)	0.11

Abbreviations: NCCN, National Comprehensive Center Network; RT, radiotherapy; WBRT, whole-breast radiotherapy.

for hypofractionation but were ultimately treated with a traditional schedule.

All WBRT was delivered using 3DCRT. No cases used an IMRT technique. WBRT was delivered in 2.66 or 2.67 Gy/fraction for the hypofractionated regimen and 2 Gy/fraction for the traditional regimen.

Direct medical cost estimates were as follows: 15 fractions of 3DCRT, \$7,197.87; 15 fractions of IMRT, \$11,232.33; 25 fractions of 3DCRT, \$9,731.39; and 25 fractions of IMRT, \$16,877.45 (Table 2).

Discussion

Among patients with early-stage breast cancer who had WBRT at our NCCN member institution, the hypofractionation rate

increased from 14% in 2006–2008 to 74% in 2011–2013 (Figure 1). These hypofractionation rates compare favorably to national rate trends, including the subset of academic institutions. An analysis based on the Surveillance, Epidemiology, and End Results (SEER)-Medicare-linked database showed hypofractionation rates of 10% in 2008 and 14% in 2009–2010 for early-stage breast cancer.²¹ Retrospective data from the National Cancer Database demonstrated that for patients deemed eligible for hypofractionation, national hypofractionation rates increased from 10% in 2008 to 23% in 2011, with increasing rates of hypofractionation in academic institutions from ~16% in 2008 to ~32% in 2011.²² More recently, a report from the Michigan Radiation Oncology Quality Consortium showed that 31% of patients

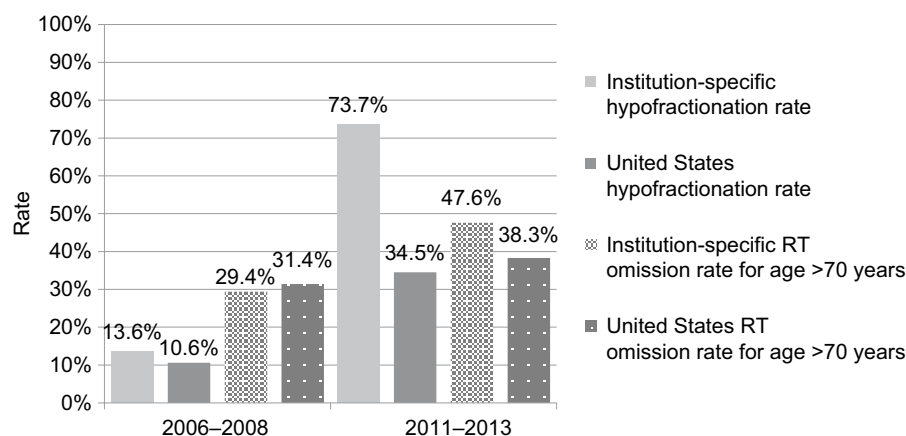


Figure 1 Rates of hypofractionation and RT omission for the years 2006–2008 and 2011–2013. WBRT hypofractionation rates are for patients aged ≥50 years with hormone receptor-positive, early-stage breast cancer. RT omission rates are for patients aged >70 years. Rates at our NCCN-member institution are compared to national rates per Bekelman et al²⁴ and Palta et al.²⁵ $P < 0.001$ for statistical difference between the 2006–2008 and 2011–2013 institution-specific hypofractionation rates. $P = 0.11$ for statistical difference between the 2006–2008 and 2011–2013 institution-specific RT omission rates.

Abbreviations: NCCN, National Comprehensive Center Network; RT, radiotherapy; WBRT, whole-breast radiotherapy.

Table 2 Direct medical cost for whole-breast radiotherapy

Code	Description	Technical cost (\$)	Professional cost (\$)	Total cost (\$)	3DCRT		IMRT	
					15 fractions	15 fractions	25 fractions	25 fractions
77263	Clinical treatment planning, complex	–	167.56	167.56	1	1	1	1
77280	Simulation, simple	166.65	36.52	203.17	1	–	1	–
77290	Simulation, complex	291.77	81.99	373.76	1	–	1	–
77293	Respiratory motion management	–	104.91	104.91	0.5	–	0.5	–
77295	3DCRT treatment plan	1,026.81	224.13	1,250.94	1	–	1	–
77300	Dosimetry calculation	107.40	32.58	139.98	2	2	2	2
77301	IMRT treatment plan	1,026.81	417.84	1,444.65	–	1	–	1
77321	Electron boost plan	291.77	49.77	341.54	–	–	–	–
77334	Treatment devices	291.77	64.81	356.58	3	1	3	1
77336	Weekly physics	107.40	–	107.40	3	3	5	5
77338	Design MLC for IMRT	291.77	224.13	515.90	–	1	–	1
77385	IMRT treatment delivery, simple	505.51	–	505.51	–	15	–	25
77412	3DCRT/electron treatment delivery	194.35	–	194.35	15	–	25	–
77417	Weekly port films	NC	–	–	3	–	5	–
77427	Weekly RT management	–	187.61	187.61	3	3	5	5
Direct medical cost (\$)					7,197.87	11,232.33	9,731.39	16,877.45

Abbreviations: –, not applicable; 3DCRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; MLC, multileaf collimator; NC, no charge; RT, radiotherapy.

with early-stage breast cancer registered from October 2011 to December 2013 received hypofractionated WBRT.²³ A retrospective analysis using administrative claims data from commercial health care plans covering 7% of the adult female population in the USA showed that the rates of hypofractionated WBRT for women aged ≥ 50 years with early-stage breast cancer were 11% in 2008 and 35% in 2013.²⁴ While these comparisons show a trend toward increased hypofractionation nationwide, our institution seems to have adopted the shorter treatment schedule to a far greater extent.

RT omission for patients aged >70 years with early-stage breast cancer increased by nearly 20% between the two periods we evaluated at our institution (29%–48%, Figure 1). According to a SEER database analysis, national rates of RT omission for this group were 31% between 2000 and 2004 and 38% between 2005 and 2009.²⁵ As of 2011–2013, the rate of RT omission for women aged >70 years at our institution exceeds the published national rates. Based on CALGB 9343,¹² current NCCN guidelines¹³ use age 70 years as a cutoff for the selected option of RT omission. However, multiple additional trials are now evaluating RT omission for younger patients who are still at low risk of recurrence. PRIME II has published 5-year data on RT omission for patients aged ≥ 65 years.²⁶ Ongoing studies include the IDEA Study²⁷ (postmenopausal patients), the PRECISION Trial²⁸ (patients aged ≥ 50 years), and the EXPERT Trial²⁹ (patients aged ≥ 50 years). If long-term results from these trials are favorable, RT omission may become an option for even younger patients.

Of the 16 patients who received the traditional schedule WBRT from 2011 to 2013, six patients preferred the longer schedule and five had a large breast separation, which has been a perceived contraindication to hypofractionated WBRT.⁶ Thus, only five of 88 patients were treated with the longer traditional radiation schedule without a clearly documented rationale for not using the shorter hypofractionated schedule. Although the OCOG trial excluded women with a maximum width of breast tissue of over 25 cm, the START trials had no breast separation limitations.^{6–8} Other studies have shown larger body habitus (proxy for large breast separation) to be associated with lack of hypofractionation.^{21,23} IMRT may be an appropriate modality to minimize adverse effects for patients with large breast separation who are undergoing hypofractionation, thus broadening the applicability of the hypofractionated schedule.³⁰

Factors associated with higher hypofractionation rates include both patient and institutional characteristics, such as living ≥ 50 miles from the cancer reporting facility,²²

treatment at an academic center,²² higher median income,^{22,24} older age,^{21,23,24} higher education level, living in a western SEER region, and more comorbidity.²¹ Bekelman et al²⁴ also found hypofractionation more likely to occur in an outpatient hospital setting versus a freestanding facility. Our institution is a tertiary academic center in the western USA that spans both outpatient hospital and freestanding facilities. Although we did not investigate these patient demographic characteristics, it is possible that the patient population in our study is unbalanced with regard to the abovementioned variables, resulting in selection bias.

In contrast to the slower national uptake of hypofractionated WBRT and the selected option of RT omission, IMRT has shown rapid acceptance despite limited supportive evidence. Among patients with node-negative breast cancer, IMRT use in breast conservation increased from 9% in 2004 to 23% in 2009 to 2010.²¹ IMRT was not used at our institution for patients aged ≥ 50 years with hormone receptor-positive, early-stage breast cancer. Some providers argue that IMRT can deliver a more homogeneous radiation dose and thus reduce toxicity. However, our practice is to use field-in-field 3DCRT technique, which achieves dose homogeneity comparable to inverse-planned IMRT.³¹ Although hypofractionated regimens and RT omission reduce cost, IMRT is more costly than 3DCRT.¹⁴ At current reimbursement levels, IMRT is associated with an estimated added cost of \$4,034.46 and \$7,146.06 for 15- and 25-fraction WBRT courses, respectively (Table 2). Whether providers are making a conscious effort or not, it would stand to reason that financially advantageous practices, such as the use of IMRT, would be used more commonly than their cheaper counterparts. This type of financial incentive has been previously demonstrated for IMRT use among self-referring urologists³² and may similarly impact national IMRT utilization, as well as lack of hypofractionation and RT omission in early-stage breast cancer.

Potential cost savings may be substantial if providers follow evidence-based practice guidelines and expert recommendations for selected patients with early-stage breast cancer. According to the ASTRO evidence-based guidelines, each year, about 20,000 women who have WBRT are eligible for hypofractionation. About 2,000 of these patients ultimately receive IMRT. About 4,000 are aged >70 years and eligible for RT omission.²⁴ By our own assessment (Table 2), the direct medical cost of a single course of WBRT using 15 fractions 3DCRT is less than half the cost of 25 fractions IMRT, a savings of nearly \$10,000 in direct medical costs per patient by selecting hypofractionated 3DCRT over traditional course IMRT. RT omission removes the cost of RT entirely,

a savings of about \$7,000–\$17,000 per patient. Practice patterns with regard to WBRT for early-stage breast cancer affect thousands of patients per year, who could each save thousands of dollars in direct medical costs if hypofractionation or RT omission is chosen. Given these data, choosing hypofractionated WBRT when appropriate, omitting RT for selected elderly women, and avoiding unnecessary IMRT could ultimately account for millions of dollars in direct medical cost savings to the US healthcare system – all while adopting evidence-based practices.

Limitations

Limitations of the current study include the small sample size and its retrospective nature. Our institution is an NCCN member that establishes institutional guidelines across three national sites and may, therefore, stand as an outlier among national RT providers. There are additional scenarios beyond the scope of this paper, including longer treatment schedules using 1.8 Gy/fraction or lumpectomy cavity boost, or both, which add time, fractions, and expenses. Our institution uses the Radiation Therapy Oncology Group 1005 indications for lumpectomy cavity boost as a guideline, which spares many patients' additional fractions. Additional studies have evaluated even shorter regimens, delivering five fractions once weekly³³ or five fractions in 1 week.³⁴ We understand that practice patterns may vary nationally and have only presented the direct medical costs associated with the four WBRT regimens most applicable to our discussion.

Conclusion

Overall, the data presented show that it is possible for RT practice patterns to rapidly change in response to new level I evidence. We demonstrate evidence-based practice and adherence to national expert recommendations for the population of women aged ≥ 50 years with hormone receptor-positive, early-stage breast cancer. Millions of potential savings in the health care system could be achieved by practicing evidence-based medicine and following national guidelines for RT in early-stage breast cancer. More importantly, shorter treatment schedules and omission of WBRT in selected patients do not compromise oncologic outcomes and have the immeasurable benefit of avoiding weeks of potentially unnecessary RT to patients.

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Disclosure

The authors report no conflicts of interest in this work.

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