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ORIGINAL ARTICLE – BREAST ONCOLOGY

Meta-Analysis of Local Invasive Breast Cancer Recurrence After Electron Intraoperative Radiotherapy

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ABSTRACT

Background. Electron intraoperative radiotherapy (IORT) can be used during breast conserving surgery to treat early-stage invasive breast cancer. Using data from current clinical and observational studies, this study aimed to assess the impact of single-fraction electron IORT on local recurrence rates.

Methods. Studies on single-fraction electron IORT during breast conserving surgery were identified through a search of PubMed and Google Scholar, as well as through secondary referencing. Local recurrence rate was the main outcome of interest. A meta-analysis of proportions using a binomial distribution to model the within-study variability and a random effects model was conducted to estimate a pooled local recurrence rate. To estimate a 5-year recurrence rate, a single-sample Poisson-normal model was applied to model the probability of events occurring during a fixed period (60 months).

Results. The study identified 13 publications. The analysis demonstrated a pooled monthly local recurrence rate of 0.02% per person-month (95% confidence interval CI 0.00–0.06%) for the studies with a follow-up period shorter than 5 years, 0.03% per person-month (95% CI 0.02–0.06%) for studies with a follow-up period of 5 years or longer, and 0.02% per person-month (95% CI 0.01–0.04%) overall. Based on this model, the predicted 5-year local recurrence rate was 2.7% (range 1.9–3.7%).

Conclusions. According to the published literature, the rate of breast cancer local recurrence after electron IORT was 0.02% per person-month, with an adjusted 5-year recurrence rate of 2.7%. These findings support the recent guidelines from the American Society for Radiation Oncology (ASTRO) supporting the use of electron IORT for low-risk patients.

Breast cancer represents the most common non-cutaneous cancer among women in industrialized nations, with an estimated 250,000 new cases in the United States alone in 2016.[1,2] Early-stage disease represents the majority of new breast cancer diagnoses, with treatment options including mastectomy and breast-conserving therapy (BCT). To date, multiple randomized studies and meta-analyses have demonstrated no difference in outcomes between mastectomy and BCT, with a recent SEER study demonstrating better breast cancer-specific survival for patients undergoing BCT than for those receiving mastectomy with or without radiation.[3–6]

Traditionally, adjuvant radiation after breast-conserving surgery has consisted of standard fractionated whole-breast irradiation (WBI) with or without a boost, requiring patients to undergo 5–7 weeks of daily treatments. More recently, hypofractionated WBI has emerged as a standard of care alternative, but still requires 3–4 weeks of daily treatment.[7,8] Partial-breast techniques, including accelerated partial-breast irradiation (APBI) and intraoperative radiation therapy (IORT), have been developed during the past several decades based on patterns of failure data suggesting that the lumpectomy cavity and a margin surrounding it represents the primary target of adjuvant radiation therapy to prevent the majority of local recurrences.[9] While APBI can reduce treatment duration to

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1 week or less, IORT allows for treatment to be completed in a single fraction at the time of surgery in most cases.[10,11] Recent studies have demonstrated that these alternatives, including partial-breast techniques, can be offered to a large percentage of patients with early-stage breast cancer based on current guidelines and trial inclusion criteria.[12]

Intraoperative radiation therapy can be delivered using electrons or low-energy X-rays and can not only shorten the duration of treatment, but can also potentially reduce side effects and improve cosmetic outcomes. Although IORT may be an attractive alternative to traditional postoperative radiotherapy for many low-risk early-stage patients, its effectiveness in preventing local recurrences remains a concern based on higher rates of local recurrence seen in two randomized trials.[10,11] Previous studies have evaluated APBI or low-energy IORT, but electron and low-energy X-ray IORT differ significantly in terms of technique and dosimetry.[13] Therefore, this study aimed to evaluate the impact of single-fraction electron IORT (excluding low-energy X-ray IORT) on local recurrence rates using data from published studies.

MATERIALS AND METHODS

Literature Review

Relevant publications were identified through searches of the online databases PubMed and Google Scholar. For PubMed, the search terms used included "single fraction," "single dose," "electrons," "intraoperative radiotherapy," "intraoperative radiation," "radiation therapy," "breast neoplasms," "breast cancer," and "IOERT." The search string for PubMed contained the following: "single"[All Fields] AND (fraction[All Fields] OR dose[All Fields]) AND ("electrons"[MeSH Terms] OR "electrons"[All Fields] OR "electron"[All Fields]) AND intraoperative[All Fields] AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR ("radiation"[All Fields] AND "therapy"[All Fields]) OR "radiation therapy"[All Fields] OR "radiotherapy"[MeSH Terms] OR ("radiation"[All Fields] AND "therapy"[All Fields]) OR "radiation therapy"[All Fields]) AND ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms" All Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields])) AND ("humans"[MeSH Terms] AND English[lang]). A second search string was as follows: IOERT[All Fields] AND ("breast"[MeSH Terms] OR "breast"[All Fields]). Google Scholar was also searched using the search terms "single fraction or dose," "electrons," "intraoperative radiotherapy," and "breast cancer."

To supplement the electronic database searches, a review of the referenced articles within each of the included publications was completed, and some gray literature was considered, namely, poster presentations and conference proceedings providing unpublished updates from previously published studies. The main outcome of interest was local recurrence. The inclusion criteria specified presence of invasive breast cancer, single-fraction IORT, and electron-based IORT. The exclusion criteria ruled out postsurgical WBI, mastectomy, X-ray-based IORT, administration of IORT before excision, and dosimetry studies.

Data were extracted from each of the included studies regarding the characteristics related to the study, protocol, patients, efficacy including cosmesis, and safety/toxicity. Information was collected on the inclusion and exclusion criteria for each publication, allowing the appropriateness of the sample selection to be explored and comparisons to be drawn between the patient populations and the American Society for Radiation Oncology (ASTRO) and European Society for Therapeutic Radiology and Oncology (ESTRO) guidelines. Both the ASTRO and ESTRO guidelines are provided in Table 1. Publications were clustered by research group to ensure the identification of overlapping patient samples.

During the review, it became clear that some studies also reported on patient safety/toxicity and patient satisfaction outcomes, such as toxicity and cosmesis. Given the importance of these outcomes, the decision was made to abstract and consider the appropriateness of a meta-analysis for summarizing these additional outcomes.[14]

Statistical Analysis

After qualitative review of the studies, it was determined that meta-analysis would be an appropriate tool for providing a pooled summary estimate of the available data on local recurrence rate, but not for determining toxicity and cosmesis. To obtain a pooled estimate of the main outcome of interest (local recurrence), the Metaprop package in Stata software (version 13) was used.

A random-effects meta-analysis of proportions model using the Dersimonian and Laird method was run to calculate an overall pooled recurrence rate as well as recurrence rates within two study subgroups: those with a follow-up period shorter than 5 years versus those with a follow-up period of 5 years or longer. However, because the majority of the available studies did not follow tumor recurrence rates after 5 years, it was difficult to estimate a reliable and statistically sound 5-year recurrence rate. This was further complicated by the presence of zero events (no recurrences) in some studies, particularly those with small samples. For these reasons, single-sample, random-effects

TABLE 1 ASTRO/ESTRO guidelines

	ASTRO guidelines 2009			GEC-ESTRO guidelines 2010		
Factor	Suitable	Cautionary	Unsuitable	Good	Possible	Contraindicated
Age (years)	≥ 60	50–59	< 50	> 50	> 40–50	≤ 40
BRCA 1, 2 mutation	Absent	Absent	Present	–	–	–
Tumor size (cm)	≤ 2	2.1–3.0	> 3	pT1–2 (≤ 30 mm)	pT1–2 (≤ 30 mm)	pT2 (> 30 mm), pT3, pT4
pT	pT1	pT0 or pT2	pT3–pT4	pT1–2	pT1–2	pT2, pT3, pT4
Margins	Negative (≥ 2 cm)	Close (< 2 mm)	Positive	Negative (≥ 2 mm)	Negative, but close (< 2 mm)	Positive
Grade	Any	Any	Any	Any	Any	–
LVSI	No	Limited/focal	Extensive	Not allowed	Not allowed	Present
ER status	Positive	Negative	–	Any	Any	–
Multicentricity	Unicentric	Unicentric	Present	Unicentric	Unicentric	Multicentric
Multifocality	Unifocal (≤ 2 cm)	Unifocal (2.1–3.0 cm)	Multifocal (> 3)	Unifocal	Multifocal (limited within 2 cm of the index lesion)	Multifocal (> 2 cm from the index lesion)
Histology	IDC	Invasive lobular	Any	IDC, mucinous, tubular, medullary, and colloid mL	IDC, mucinous, tubular, medullary, and colloid mL.	–
Pure DCIS	Not allowed	≤3 cm	>3 cm	Not allowed	Allowed	–
EIC	Not allowed	≤ 3 cm	> 3 cm	Not allowed	Not allowed	Present
Nodal stage	pN0 (i^-, i^+)	pN0 (i^-, i^+)	pN1, pN2, pN3	pN0 (by SLNB or ALND)	pN1mi, pN1a (by ALND)	pNx; ≥ pN2a (4 + positive nodes)
Nodal surgery	SLNB or ALND	SLNB or ALND	Not performed	SLNB or ALND	ALND	–
Neoadjuvant therapy	Not allowed	Not allowed	If used	Not allowed	Not allowed	If used
ILC	Not allowed	Allowed	Allowed	Not allowed	Allowed	–
Associated LCIS	Any	Any	Any	Allowed	Allowed	–

ASTRO American Society for Radiation Oncology, *ESTRO* European Society for Therapeutic Radiology and Oncology, *GEC* Groupe Europeen de Curietherapie, *LVSI* lymphvascular space invasion, *ER* estrogen receptor, *IDC* invasive ductal carcinoma, *DCIS* ductal carcinoma in situ, *EIC* extensive intraductal component, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection, *ILC* invasive ductal carcinoma, *LCIS* lobular carcinoma in situ

Poisson-normal modeling[15–17] for the meta-analysis of incidence rates was used to control for study follow-up time, enabling reliable estimation of a 5-year recurrence rate.

RESULTS

The initial literature search was conducted in August of 2015 using the specified search terms. The first PubMed search string generated 30 results, and the second search string generated 29 results. The Google Scholar search generated 6830 results. The top 100 of these were reviewed, with 30 publications examined for eligibility. After application of the inclusion and exclusion criteria, 13 studies were considered eligible to be included in the analysis.

The inclusion criteria for each article were compared with the ASTRO and ESTRO guidelines, as shown in Table 2. With the exception of age, all the included studies mainly followed the ASTRO guidelines with respect to data available. Due to the small sample size of eligible studies, sub-analysis by ASTRO consensus grouping was not performed.

Each study was abstracted for key data (Tables 3, 4).[11,18–29] Studies were excluded if they were a summary or an analysis of previously published data, used boost rather

TABLE 2 Application of ASTRO/ESTRO guidelines to included studies

Factor	Veronesi et al.[11]	Mussari et al.[25]	Frasson et al.[20]	Lemanski et al.[24]	Dall'Oglio et al.[19]	Phillippson et al. [27]	Rocco et al.[28]	Hershko et al.[22]
Age (years)	48–75	> 45	> 45	≥ 65	≥ 50	≥ 40	< 75	> 50
BRCA 1, 2 mutation	–	–	–	–	NA	–	–	–
Tumor size (cm)	≤ 2.5	≤ 2	< 2.5	≤ 2	≤ 3	≤ 2	≤ 2.5	≤ 2.5
pT	–	pT1	pT1	pT0–pT1	T1–2	–	–	–
Margins	–	Negative	–	Negative (≥ 2 mm)	–	–	–	–
Grade	–	–	–	Any	Any	Any	Any	Any
LVSI	–	–	NA	–	NA	–	–	–
ER status	Any	Positive	–	Positive	Any	Any (hormone receptor type)	–	–
Multicentricity	–	Unicentric	–	Unicentric	Unicentric	–	Unicentric	"single"
Multifocality	–	Unifocal	Unifocal	Unifocal	Unifocal	Unifocal (via preop MRI)	Unifocal	Unifocal
Histology	Invasive ductal or lobular	–	Invasive ductal carcinoma, lobular invasive, medullar	Invasive ductal carcinoma	Invasive ductal carcinoma mucinous, medullary, tubular, colloid	Invasive ductal, tubular, colloidal, mucinous, or medullary	Invasive ductal carcinoma	Invasive ductal carcinoma
Pure DCIS	–	Not allowed	–	–	Not allowed	–	Not allowed	Not allowed
EIC	–	Not allowed	–	Allowed	Not allowed	–	Not allowed	–
Nodal stage	–	pN0	–	pN0	NA	No lymph node involvement	pN0	No lymph node involvement
Nodal surgery	–	SLNB, ALND	SNLB, ALND	ALND	–	–	SLNB	SLNB
Neoadjuvant therapy	–		–	Not allowed	Not allowed	–	–	–
ILC	–	–	Allowed	Not allowed	–	–	Not allowed	Not allowed
Associated LCIS	–	Not Allowed	–	Not allowed	Allowed	–	Not allowed	–

Age (years)	Osti et al.[26]	Hanna et al.[21]	Wang et al.[29]	Cedolini et al.[18]	Kawamura et al.[23]
BRCA 1,2 mutation	> 50	> 40		18–80	> 50
Tumor size (cm)	< 2	< 3	< 3	< 3	< 2.5
pT	–	–	–	–	–
Margins	–		–	> 5 mm	Negative
Grade	–	–	–		–
LVSI	–	–	–	–	–

TABLE 2 continued

Age (years)	Osti et al.[26]	Hanna et al.[21]	Wang et al.[29]	Cedolini et al.[18]	Kawamura et al.[23]
ER status	–	–	–	–	–
Multicentricity	–	Unicentric	–	Unicentric	–
Multifocality	–	–	Unifocal	Unifocal	–
Histology	–	–	–	Invasive ductal	–
Pure DCIS	Not Allowed	Not allowed	–	–	–
EIC	Not allowed	EIC < 3 allowed		–	–
Nodal stage	–	Negative node status	pN0-1 included	pN0-1mi	–
Nodal surgery	–	–	–	–	–
Neoadjuvant therapy	–	–	–	–	–
ILC	–	–	–	–	–
Associated LCIS	–	–	–	–	–

ASTRO American Society for Radiation Oncology, *ESTRO* European Society for Therapeutic Radiology and Oncology, *LVSI* lymphovascular space invasion, *NA* not available, *ER* estrogen receptor, *DCIS* ductal carcinoma in situ, *EIC* extensive intraductal component, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection, *ILC* invasive ductal carcinoma, *LCIS* lobular carcinoma in situ

than single IORT, or did not report the primary outcome of interest (local recurrence rates). It is important to note that the ELIOT and TARGIT-A trials currently are the only two randomized trials that test the effectiveness of intraoperative partial breast radiotherapy, but the techniques are quite different.[10,11] The TARGIT trial delivers radiation in the form of low-energy X-rays, whereas the ELIOT trial delivers electron-based radiation to the tumor bed with the aid of a pectoral lead shield.

To establish a homogeneous comparison and analysis, only studies that discussed intraoperative partial breast radiotherapy with electrons were included. With the exception of the phase 3 ELIOT trial, all the studies were either phase 2 or observational single-institution experiences. In terms of publication status, 12 studies were published as peer-reviewed manuscripts, and 1 was a conference abstract.

The mean follow-up of the 13 studies included, as reported by individual studies, ranged from 17.7 to 72 months. The nine studies with a follow-up period shorter than 5 years had a combined sample size of 853 patients, whereas the remaining four studies with follow-up periods of 5 years or longer had a combined sample size of 798 patients.

Overall, the patient populations demonstrated consistent features (Tables 3, 4). Tumors were predominantly grade 2 (42–64% of the study populations). The majority of the cancers (74–100%) were node-negative, and invasive ductal carcinoma was the primary cancer subtype observed (23–100%). Most patients from these studies underwent similar surgical procedures. Most of the protocols aimed to administer an average dose of 21 Gy, with an average across the 13 groups of 21.1 Gy (median, 21 Gy).

The local recurrence rates among the included studies can be found in Table 3. The meta-analysis demonstrated a pooled monthly local recurrence rate of 0.02% per person-month (95% confidence interval CI 0.0–0.06%) for the studies with a follow-up period shorter then 5 years (number of patients, 851), 0.03% per person-month (95% CI 0.02–0.06%) for the studies with a follow-up period of 5 years or longer (number of patients, 798), and 0.02% per person-month (95% CI 0.01–0.04%) overall (Fig. 1). Applying a Poisson-normal model predicted a 5-year recurrence rate of 2.7% (95% CI 1.9–3.7%) (Fig. 2).

Data on cosmesis and toxicity were not graded consistently across studies. Some reports summarized these outcomes by numeric grading systems (CTCAE, LENT-SOMA), providing a qualitative assessment listing specific outcomes such as necrosis, and other publications did not consider these outcomes at all. Given the substantial heterogeneity of the outcomes across studies, it was determined that a meta-analysis based on cosmesis and toxicity outcomes would not be appropriate. The studies

TABLE 3 Study and treatment characteristics

Author	Study type	Years	No. of patients	Mean follow-up (months)	Adjuvant therapy (%)	Dose (Gy)	Technique	Local recurrence rate per study follow-up time (%)
Cedolini et al.[18]	Phase 2	2005–2009	73	69.5	Chemotherapy (13) Endocrine therapy (85)	21	Lead/aluminum; margins > 5 mm	1 yr (0.8) 3 yr (0.8) 5 yr (0.8) 6 yr (2.0)
Dall'Oglio[19]	Phase 2	2006–2009	226	51	NA	21	Lucite disk	1.80%
Frasson et al.[20]	Observational	2004–2005	40	17.7	NA	21	Lead/aluminum; margins ≥ 10 mm	2.50%
Hanna et al.[21]	Phase 2	2004–2009	152	50.7	Chemotherapy(46) Endocrine therapy (90)	21	Lead/aluminum/ Silicone; margins > 20 mm	3.70%
Hershko et al.[22]	Observational	2006–2010	27	36	Chemotherapy (13) Endocrine therapy (100) Both (13)	21	Lead; margins > 2 mm	0.00%
Kawamura et al.[23]	Phase 2	2007–2010	32	65	Chemotherapy (9) Endocrine therapy (69) Both (6) None (16)	19–21	Acrylic resin	0.00%
Lemanski et al.[24]	Phase 2	2004–2007	42	72	NA	23	Not reported; margins > 20 mm	7.10%
Mussari et al.[25]	Phase 2	2000–2002	47	48	NA	22.6	Lead/aluminum; margins ≥ 10 mm	0.00%
Osti et al.[26]	Phase 2	2007–2011	110	27	Chemotherapy (24) Endocrine therapy (88) Both (20) None (8)	21	Lead/aluminum; margins 15–20 mm	2.70%
Phillippson et al.[27]	Phase 2	2010–2012	200	23.3	Chemotherapy (5) Endocrine therapy (82) Both (12) None (2)	21	Lead/aluminum; margins 10–20 mm	0.00%
Rocco et al.[28]	Observational	2009–2010	13	46	Chemotherapy (8) Endocrine therapy (62) Both (31)	21	Lead/aluminum; margins ≥ 10 mm	0.00%
Veronesi et al.[11]	Phase 3	2000–2007	651	65	Chemotherapy (8) Endocrine therapy (75) Both (13) None (4)	21	Lead/aluminum	5.38%
Wang et al.[29]	Phase 2	2008–2012	36	51.8	Chemotherapy (67) Endocrine therapy (8.3)	20	Lead disk	4.00%

NA not available

reporting on cosmesis outcomes showed high patient satisfaction,[18,20] with 67.7–92.8% reporting an excellent or good cosmesis.[21–29] In studies reporting CTCAE toxicities, grade 1 toxicity ranged from 4 to 7%, grade 2 toxicity ranged from 0 to 9%, and grade 3 toxicity ranged from 0 to 4%.[19,21,23,25,27] Fibrosis usually was reported using the LENT SOMA scale, ranging from 1 to 24% for grade 1 fibrosis, from 0 to 30% for grade 2 fibrosis, and from 0 to 8% for grades 3 and 4 fibrosis.[19,21,23,25–28]

DISCUSSION

The results from the current meta-analysis of 13 studies demonstrated low rates of local recurrence (0.02% per person-month), with an adjusted 5-year recurrence rate of 2.7% using electron IORT (for all risk groups of patients). Although a large proportion of the patients came from the ELIOT trial, which showed higher rates of local recurrence than WBI, it should be noted that a subset analysis from this study demonstrated low rates of local recurrence when high-risk patients were excluded.[11,30] These rates are as good as or better than those traditionally seen after breast-conserving surgery with adjuvant WBI, although the follow-up evaluation for the cohort was limited. For example, the Early Breast Cancer Trialists' Collaboration (EBCTG) meta-analysis found a 12.6% rate of recurrence after 5 years.[5] The reduced rate of local recurrence observed in the current study (and in more contemporary studies of

TABLE 4 Patient and tumor characteristics

Author	Median patient age years (range)	Median tumor size mm (range)	Grade (%)	Axillary staging (%)	Node-positive (%) (*n*)	Margins (%)	Reexcision rate (%)
Cedolini et al.[18]	Mean: 63.62 ± 7.43		G1 (43) G2 (42) G3 (15)	ALND (4) SLNB (96)			Margin widening (4.1) Mastectomy (2.7)
Dall'Oglio et al.[19]							
Frasson et al.[20]	Mean: 63 (45–80)	15 (5–30)		20	20 (8)		Core biopsy (5) Surgery (5)
Hanna et al.[21]	58.3 (40–85.4)	pT1: 87.5% pT2: 12.5%	G1 (9) G2 (52) G3 (39)		12 (18)	2	Surgery due to complication (3.9)
Hershko et al.[22]	68 (50–83)	≤ 10: 45% 11–20: 52% > 20: 3%	G1 (32) G2 (52) G3 (16)		6.5 (2)	0	
Kawamura et al.[23]	72 (30–84)	Tis: 9% < 10: 41% 10–20: 47% > 20: 3%	G1–G2 (88) G3 (13)	12.5	13 (4)	Excluded	
Lemanski et al.[24]	72 (66–80)		G1–G2 (86)				Salvage mastectomy (9.5)
Mussari et al. [25]	63 (46–79)	≤ 5: 6% 6–10: 60% 11–20: 34%	G1 (36) G2 (64) G3:		15 (7)	Excluded	
Osti et al.[26]	66 (48–87)	< 10: 45% 10–20: 40.5% > 20: 14.5%	G1 (25) G2 (45) G3 (30)	5.5	17 (19)	Excluded	Total mastectomy (3)
Phillippsonet al.[27]	61 (40–85)	< 5: 3% 6–10: 37% 11–20: 58% > 20: 2%	G1 (43) G2 (42) G3 (15)	3	7 (14)		
Rocco et al.[28]	Mean: 59 (50–72)				0		
Veronesi et al.[11]	58 (48–75)	< 10: 31% 10–15: 38% 15–20: 19% > 20: 13%	G1 (30) G2 (47) G3 (20)	26	26 (169)		
Wang et al.[29]	46.9 (26–70)	≤ 20: 80.5% > 20: 19.5%			8 (3)	0	0

ALND axillary lymph node biopsy, *SLNB* sentinel lymph node biopsy

BCT) may have been due in part to earlier-stage, low-risk cancers in this cohort of patients receiving electron IORT, or to advances in surgery, chemotherapy, and radiation therapy techniques.[5] It should be noted that the current rates of recurrence are similar to and consistent with 5-year outcomes from modern studies examining hypofractionated WBI as well as recent randomized studies evaluating APBI.[7,8,31,32]

Additionally, the rates of local recurrence were similar to those in the TARGIT trial (3451 patients, 1222 of whom had follow-up periods longer than 5 years), which used low-energy IORT and had a 5-year local recurrence rate of 3.3%, although the median follow-up period was only 29 months.[10] The rates of excellent/cosmesis, although variable, were consistent with data evaluating hypofractionated WBI or APBI.[7,29] Additionally, the toxicity rates were lower than in the WBI and APBI series to date.[33] Although the rates of fibrosis were highly variable, they were primarily for grades 1 and 2 fibrosis and may reflect

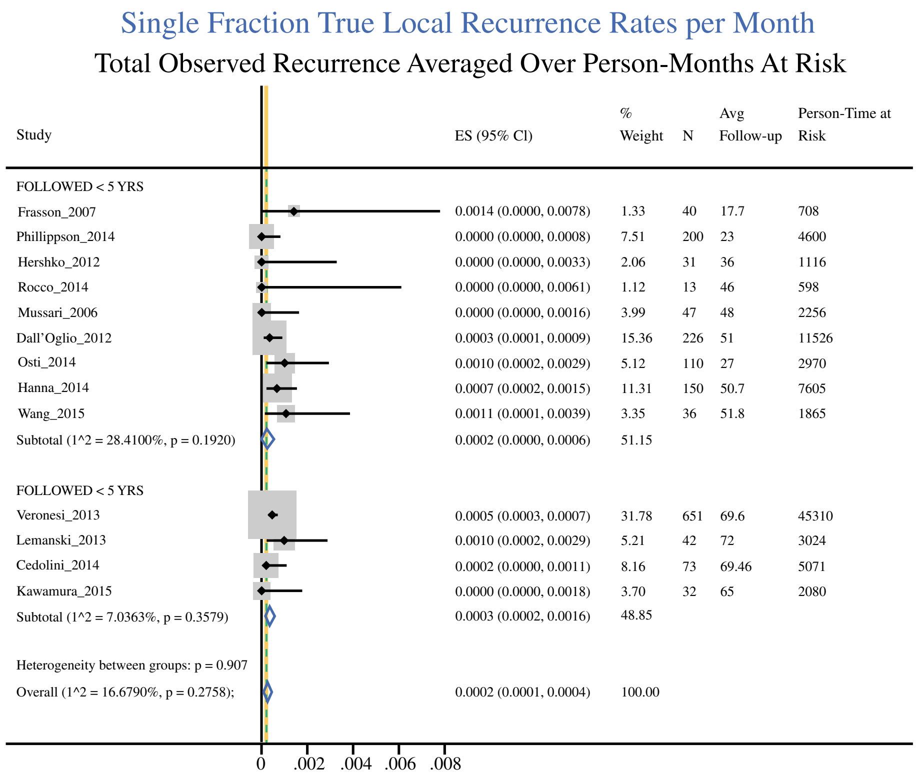

FIG. 1 Local recurrence per month by study

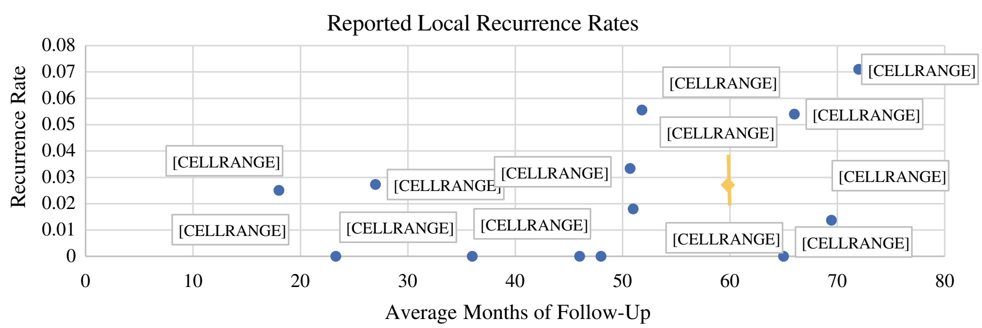

FIG. 2 Results from the meta-regression using a standardized 5-year prediction of recurrence rates

the subjectivity of the assessment, with low rates of grade 3 fibrosis consistently noted.

Although the results from this meta-analysis were "good" overall, they were based upon a heterogeneous group of patients, some of whom may not have been candidates for IORT based on current guidelines. Additionally, the follow-up period was short, and there is potential for late recurrences with a predominantly estrogen receptor-positive cohort of patients. Therefore, until additional data are published, it seems prudent to follow the recent guidelines for the application of IORT provided by ASTRO (see later) and to limit the use of electron IORT to the lower-risk category of patients defined as "suitable" for the application of APBI off protocol.

Statistical Analysis Rationale

Due to significant variability in follow-up periods, single-sample, Poisson-normal modeling for the meta-analysis of incidence rates was used to derive a predicted 5-year recurrence rate, with control for study follow-up time. Such techniques for varying follow-up times and heterogeneity in effect reduce the chance of bias introduced through the application of typical techniques used in meta-regression analyses and have been used previously, including their use in published analyses evaluating radiation-induced thyroid cancers and catheter-related line infections.[16,17,34]

Rationale for IORT

One of the challenges with breast-conserving therapy has been the duration of adjuvant radiation, with studies documenting significant numbers of patients who fail to receive adjuvant radiation therapy.[35–37] Additionally, data have demonstrated that the risk of recurrence for patients varies based on patient and pathologic factors allowing for adjuvant radiation to be risk-stratified with patients offered endocrine therapy alone, IORT, APBI, hypofractionated WBI, or standard fractionated APBI based on individual patient factors.[38]

For appropriately selected patients, IORT represents an attractive option because surgery and radiation therapy are completed in one visit, although some patients may require additional radiation therapy.[10] Compared with endocrine therapy alone, which may be an option for some patients receiving IORT, level 1 data are not available, but the current data suggest that IORT offers a reduction in rates of local recurrence.[39] Additionally, such an approach may reduce the cost of breast cancer treatment for patients and payers alike.[40]

Moving forward, future studies aim to evaluate tumor genetics for better identification of patients suitable for IORT.[41] However, at this writing, compared with alternative adjuvant radiotherapy options (hypofractionated WBI, APBI), electron IORT is situated to treat patients with low-risk, early-stage breast cancers, consistent with current ASTRO guidelines.

ASTRO Consensus Panel Guidelines for APBI

The most recent update of the ASTRO Consensus Panel guidelines on the appropriate use of APBI addressed (for the first time) the use of IORT as a partial-breast technique. The published guidelines state: "Patients interested in cancer control equivalent to that achieved with WBI post-lumpectomy for breast conservation should be counseled that in two clinical trials the risk of IBTR was higher with IORT."[42] Additionally, the guidelines note that the use of electron IORT should be restricted to suitable partial-breast irradiation (PBI) patients (age $>$ 50 years, negative margins, T1/low-risk ductal carcinoma in situ [DCIS], estrogen receptor-positive status) based on the Leonardi et al.[30] study, which showed low rates of recurrence for suitable-risk patients treated with electron IORT, whereas low-energy IORT should be used within the context of a prospective registry or trial.

The studies included in the current analysis met many of the suitable criteria, and as such, the results are consistent with the recommendations.[42] The results of the current meta-analysis support the safety and efficacy of electron IORT (based on rates of local control at 5 years).

Study Limitations

This analysis had limitations. Only one study was randomized (ELIOT), with the remaining studies either single-arm prospective analyses or observational, single-institution studies. This hindered the ability to make direct comparisons between the recurrence rates after treatment with IORT and the recurrence rate after treatment with alternative radiation options because the study populations may have been different. Additionally, outcomes beyond 5 years were not available in all the studies due to limited long-term follow-up data to date. Also, it was not possible to calculate the risk of local recurrence based on defined risk factors used in the ASTRO guidelines mentioned earlier given the limited information available in some studies. Nonetheless, this study represents the first to review electron IORT data and apply Poisson techniques to derive a clinically relevant 5-year recurrence rate after breast-preserving surgery with IORT. Future studies comparing IORT with hypofractionated WBI, APBI, or both in more select patient populations than in the ELIOT and TARGIT trials will be informative as to whether IORT during breast-conserving surgery is non-inferior to traditional external radiation therapy in preventing tumor recurrence and in identifying patient populations who may benefit most from IORT.

CONCLUSIONS

The results of this meta-analysis demonstrate a low risk of recurrence using electron IORT, with a 5-year recurrence rate of 2.7%. These outcomes support the conclusion that electron IORT is an appropriate option for low-risk patients after breast-conserving surgery. Future prospective studies are necessary to evaluate whether electron IORT is non-inferior to traditional radiation therapy options for risk-stratified groups of patients.

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