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Investigation of the effectiveness of intraoperative radiotherapy in treatment of unifocal invasive breast cancer

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ABSTRACT

Objective: Assess the 5 year local recurrence rate of intraoperative radiotherapy (IORT) in relation to the conventional treatment of external breast radiotherapy (EBRT) in eligible females diagnosed with breast cancer over age 40.

Design: Systematic literature review.

Methods: PubMed was searched using the following limits and terms: breast neoplasms, intraoperative radiotherapy, randomized control trial, clinical trial, females, English, and published in the last 10 years.

Results: Three studies were found to directly compare IORT and EBRT regarding 5 year local recurrence rates.

Conclusion: IORT was shown to be non-inferior to EBRT in two of the three studies that were examined; more research is necessary to confidently establish this. The benefits of IORT, including convenience, length of treatment, and side effect profile, deem further study worthwhile. The full risk-benefit profile of both radiotherapy options should be discussed with eligible patients in shared decision-making tailored to each individual.

INTRODUCTION

Statistics

Breast cancer is the most common cancer diagnosis among women in the United States, excluding skin cancer (1). One in eight women will develop breast cancer in their lifetime and 1 in 39 women with breast cancer will not survive (1). The commonality of breast cancer and its risk of fatality have served as motivation for researchers to investigate better treatment options.

Breast Cancer Classification

"Breast cancer" is a broad term that can be further broken down into many different classifications based on the histology and location of cancerous growth. Infiltrating ductal carcinoma (IDC) is the most common invasive breast cancer, making up 70-80% of invasive lesions, and occurs when cancerous cells begin to invade tissue outside of the ducts (2). On microscopy, IDC will appear as cords and nests of cells with varying glandular formation (2). Infiltrating lobular carcinoma (ILC) is characterized by small cells in a linear pattern invading the mammary stroma and adipose tissue (2). A combination of histologic appearance can occur where features of both IDC and ILC are present. This is referred to as mixed ductal/lobular carcinoma.

Aside from the classifications discussed above, breast cancer is also staged using the tumor, node, metastasis (TNM) classification system. T 0-4 indicates the size of the primary tumor and whether or not it has spread to the chest wall or skin of the breast (3). N 0-3 describes if the cancer has infiltrated the lymph nodes and if so, how many nodes are affected (3). M 0-1 is assigned based on whether or not the cancer has spread to distant organs (3). Clinical staging is determined before surgery based on physical exam, imaging, and biopsy results (3).

Pathologic staging is done after surgical excision of the primary tumor and is considered to be more accurate (3). The stage of the cancer helps to determine prognosis and guide treatment.

This research will focus mainly on unifocal, invasive breast cancers classified as T1-T2, N0-N1, and M0. In other words, the tumor is <5cm, has not spread beyond the axillary lymph nodes, and has not spread to distant organs. These classifications warrant treatment that traditionally includes lumpectomy of the tumor followed by radiation.

Whole breast external beam radiotherapy (EBRT)

The traditional treatment following lumpectomy includes a three to four week course of whole breast external beam radiotherapy five days a week. The patient attends15-20 sessions of radiation in the month following surgery, which can be a daunting and inconvenient task. Another drawback of this therapy includes acute toxicities of the skin, muscle, and internal organs in the area treated. Similarly, long-term complications of EBRT can include cardiotoxicity, lung injury, and secondary malignancies (4).

Intraoperative Radiotherapy (IORT)

The newest emerging option for post-lumpectomy adjuvant radiation is intraoperative radiotherapy, or IORT. With this treatment, patients receive radiation in the perioperative period, after the tumor has been removed but before the surgeon has closed the incision. It involves a single dose of radiation directly to the tumor bed over 20-45 minutes, allowing both surgery and radiation to be completed in one day (5). This negates the need for weeks of daily visits for radiation therapy, and thus can be much more convenient for the patient. Other advantages include accurate delivery of radiation directly to the tumor margins, thus decreasing the radiation effects on healthy skin and subcutaneous tissue of the breast. However, it does require increased time spent in the operating room as well as the inability to consider final pathology at the time of radiotherapy administration (5).

With these factors in mind, this research paper will focus on the efficacy of intraoperative radiotherapy compared to whole breast external beam radiotherapy in relation to five-year local cancer recurrence rates.

CLINICAL QUESTION

For women over age 40 with breast cancer, does IORT demonstrate non inferiority based on rates of local tumor recurrence within 5 years compared to traditional EBRT?

METHODS

First, a PubMed search was performed in September 2022 using the MESH term “breast cancer”, which corrected to “breast neoplasms”. Next, the key term “intraoperative radiotherapy” was added. To further refine the search results, the following criteria were selected: published in the past 10 years, randomized control trials, clinical trials, females, and English. This yielded 36 articles. 2 articles were duplicates and therefore removed. The remaining 34 articles were screened and 26 were excluded for not measuring the desired outcome of recurrence rates and/or not studying IORT. After careful reading of the 8 articles left, 4 were discarded for having a control group that differed from EBRT, having a timeline less than or greater than 5 years, or

analyzing IORT as an adjunct to EBRT instead of as the sole method of radiotherapy. The 4 articles ultimately selected contribute to answering the clinical question.

RESULTS

Study #1

Feasibility of conservative breast surgery and intraoperative radiation therapy for early breast cancer: A single-center, open randomized, prospective pilot study (6).

Objective: to analyze IORT feasibility, complications, and outcome

Study Design

The study design was a single-center, open, non-randomized, prospective pilot study that took place between January 2005 and December 2009 in Udine Italy. The endpoints measured include IORT feasibility, local recurrence rate, complications, and overall survival. All patients with invasive ductal carcinoma requiring breast conservation surgery who also met the inclusion criteria (Table 1) were offered IORT. Those who did not opt for the IORT procedure were considered as the control group. The control group also consisted of those who did not receive IORT due to technical problems.

Table 1: Inclusion Criteria Study #1
Age between 18 and 80 years old Informed consent Unifocal & unicentric disease Ductal invasive histotype Tumor size <3cm Lymph node status N0 or N1 Distance of the nearest resection margin from the tumor >5 mm by intraoperative histological examination Acceptable breast volume after quadrantectomy

Table 2: Exclusion Criteria Study #1
Presence of systemic metastasis Coexistence of a second primary tumor History of scleroderma or systemic lupus eritematodes Pregnancy Tumor localization near the areola in the central quadrant Perivascular invasion

Members of the study group underwent quadrantectomy to remove the tumor, and then IORT. However, the IORT procedure protocol differed for women <48 or ≥ 48 years old, with those <48 years old receiving adjuvant EBRT in addition to the IORT. All members of the control group received quadrantectomy, followed solely by the standard EBRT. A wide range of data were collected, as listed in Table 3.

Table 3: Data collection Study #1
Age at diagnosis BMI Familial history of breast cancer Fertility status Eventual use of estoprogestinic therapies TNM classification and stage Nuclear grading Mib1/Ki-67 proliferation index Estrogen receptor expression Progesterone receptor expression Her2/neu expression Involvement of extra-axillary lymph nodes Tumor multifocality Tumor multicentricity Extensive intraductal component Perivascular invasion Peritumoral inflammation Perinodal extracapsular invasion Blanched lymph nodes

Preoperative assessment of patients scheduled for IORT included mammography, breast ultrasound, breast MRI, chest radiography, abdominal ultrasound, and total-body bone scintigraphy. These imaging modalities are ordered to exclude multifocality, multicentricity, and systemic metastasis.

Quadrantectomy was performed on all participants and the specimen was sent for frozen-section histologic examination to confirm tumor size and measure the margins. If the tumor distance was <5 mm from the surgical resection margins, a margin enlargement was performed before IORT. The site was marked with two metallic clips on the resection bed and two on the residual mammary gland for radiologic follow up. Intraoperatively, sentinel lymph nodes were biopsied. Every excised sentinel node was then histologically examined with 3 random frozen sections submitted for immunohistochemical evaluation to look for positivity of cytokeratins, which would indicate macrometastases or micrometastases. If this was found, complete axillary lymph node dissection (CALND) was performed.

For the participants undergoing IORT, the residual mammary gland was freed from the pectoralis major muscle. A disc made of lead and aluminum was placed to minimize the radiation exposure of the chest wall, while guaranteeing full radiation dose to the target through the center of the disc. The gland parenchyma thickness was measured to calculate the energy of the electron beam required to administer the radiation dose. The target area was chosen based on tumor size and location. With the skin retracted, the sterile cylindrical applicator was introduced directly into the breast tissue with a wet gauze placed to protect the displaced skin. A polymethyl methacrylate collimator was attached onto the upper end cylinder on the mobile linear accelerator. The surgical room was evacuated before the radiation dose was administered. Patients 48 years and older were given IORT with a single dose of 21 Gy prescribed at 90% isodose curve. Those under 48 years old, received a dose of 10Gy at 100%

isodose, followed by EBRT with X photons and the first dose of 46Gy and second of 50Gy. With all cases, a plastic surgeon performed accurate hemostasis control, breast remodeling, and wound closure.

Patients in the control group had whole breast radiation beginning within 8 weeks after surgery or 4 weeks from the end of chemotherapy. The radiating dose was from 46 Gy in 23 fraction to 50 Gy in 25 fraction.

Follow-up consisted of yearly mammography and breast ultrasound for 5 years after the intervention. Data were analyzed using R (version 215.2) with significant results being $P<0.05$. Continuous variables were analyzed with one-way ANOVA or t-test while categorical variables were analyzed with Chi square test or Fisher's exact test. Local recurrence and overall survival were compared with Kaplan-Meier curves and cumulative events.

Study Results

1,214 women were treated for breast cancer during the study period with 443 of those women eligible for breast conservative surgery. Of the 443, 196 women did not meet the inclusion criteria (Table 1), leaving 247 eligible and compliant patients. Technical problems led to lack of availability of IORT and prevented 111 cases from being performed. 153 women were offered IORT, among which 81 accepted. 55 did not provide informed consent for IORT and 4 others did not have an adequate amount of breast tissue after quadrantectomy to allow for the feasibility of IORT. Ultimately, 77 eligible women were treated with IORT (4 being <48 years old and 72 ≥ 48 years old) and 170 eligible women received the standard treatment of EBRT.

No significant difference occurred between women who received IORT and those who received EBRT when looking at local tumor recurrence and overall survival. The 5 year local recurrence rate was 0.8% for women ≥ 48 years old who received IORT and 0.8% for women who received EBRT. In the 4 women <48 years old in the IORT group, no recurrences occurred. The survival rate was slightly lower in those ≥ 48 years old who received IORT compared to the control group, but the results were not statistically significant ($P=0.293$). This was due to one death of a woman from the 77 treated with IORT that developed distant metastasis during follow up.

Other outcomes measured in this study include feasibility of IORT and postoperative complications. The feasibility of IORT ended up being 95.1%. IORT was not feasible in the 4 women who had insufficient residual breast tissue after surgery. IORT was found to have significantly less complications compared to EBRT. For example, IORT usually prevented subcutaneous lesions (actinic dermatitis, lymphangitis, scar retention), chest complications (pulmonary fibrosis, nervous lesions), and pain after the procedure. However, 12 of the 77 women (15.6%) who underwent IORT suffered from wound dehiscence or fat necrosis. 1 woman of the 77 required another operation for wound toileting to be done, which is debridement and cleaning of the wound. Lastly 6 women from the IORT group needed ultrasound drainage for seroma. However, in the EBRT group, only 14.1% of women had wound dehiscence or fat necrosis. This was a significant difference ($P<0.05$).

Study Critique

Our main critique of this study is the small number of participants in the IORT group, only 77, compared to 170 women in the control group. These numbers make it difficult to accurately

compare the two groups. In addition, the lack of randomization increases the risk of selection bias, and it is unlikely that the results found in this study are representative of the entire target group. Another issue with the study is that the women less than 48 years old were given both IORT and EBRT. We cannot include these 4 women in our analysis because we are strictly comparing patients who received IORT as the only radiation therapy to patients who received the standard EBRT.

Study #2

Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomized control equivalence trial (7).

Objective: To compare local recurrence and overall survival after electron intraoperative radiotherapy with postoperative external radiotherapy

Study Design

The study was a randomized control equivalence trial performed at a single-center, the European Institute of Oncology in Milan, Italy. Patients eligible to participate were women aged 48-75 years with early breast cancer and a tumor diameter ≤ 2.5 cm who met the criteria for breast-conserving therapy. All eligible patients were randomly assigned in a 1:1 ratio to receive either external radiotherapy (EBRT) or electron intraoperative radiotherapy (ELIOT). There was no blinding.

1305 participants were enrolled in the study and randomized, with 654 assigned to external radiotherapy and 651 assigned to ELIOT. After intervention in the external radiotherapy group, 35 participants were shown to be ineligible for reasons including: benign or in-situ tumors, tumor size greater than 2.5cm, and multifocal disease. In addition, with 18 participants, protocol violations were made. This left 601 participants who received external radiotherapy following study protocol. After intervention in the ELIOT group, 50 participants were shown to be ineligible due to benign or in-situ tumors, tumor size greater than 2.5cm, metastatic disease, and multifocal disease. 16 participants violated protocol. Ultimately, 585 participants received ELIOT and followed study protocol.

Histological tumor type was assessed according to the WHO classification. The tumors were graded with the Elston-Ellis modification of the Scarff-Bloom Richardson grading system. Immunochemistry was used to assess estrogen and progesterone receptors. The HercepTest kit and immunohistochemistry was utilized to determine HER2 status. Finally, surrogate immunohistochemical markers assisted with the classification of the tumors into four molecular subtypes: luminal A, luminal B, HER 2, and triple negative.

The electron intraoperative therapy technique was performed on the experimental group using two linear accelerators, NOVAC7 and Liac. After the tumor was removed, all patients assigned to ELIOT received one full dose of 21Gy to the 90% isodose to the tumor bed. The perspex applicator tube had varying diameters depending on the tumor size and collimated the electron beam with 6-9 MeV energies. The size and site of the tumor helped determine the clinical target. The thickness of the gland was measured by a graduated needle and used to

select the energy of the electron beams. Discs made of aluminum and lead were used to protect the chest wall.

The control group received postoperative EBRT For this treatment, 50Gy were given in 25 fractions with tangential beams, followed by a boost dose of 10Gy in five fractions using a direct external electron beam.

In addition to radiotherapy, axillary dissection was performed in all patients with a positive sentinel lymph node biopsy. In patients with 3 or less positive axillary nodes, no additional intervention was needed. However, in patients with four or more positive axillary nodes, additional irradiation was required, with a fractionation of 2Gy to a total dose of 50Gy. This treatment accompanied EBRT in the control group, but was given 8-12 weeks after ELIOT in the experimental group.

Chemotherapy, endocrine therapy, and other adjuvant treatments were given according to the European Institute of Oncology policy. Follow up procedures included: a clinical examination every 3 months, an ultrasound mammary scan every 6 months, and a mammogram every year. Examinations of the lung, liver, and bone were performed as needed based on the individual's risk.

Local recurrence was defined as "the reappearance of the carcinoma at the site of surgical intervention." If a new carcinoma appeared in another quadrant of the same breast, it was called a second ipsilateral breast tumor. Ipsilateral breast tumor recurrence (IBTR) was defined as "the sum of local recurrence plus second ipsilateral tumors." A regional nodal failure occurred when the carcinoma recurred in the ipsilateral axillary, supraclavicular, or internal mammary lymph nodes. Overall survival was measured as the time from diagnosis to the last follow up or time of death. Lastly, side effects were scored using the Late Effect of Normal Tissue- Subjective Objective Management Analytic criteria.

The main outcome measured was IBTR and the secondary outcome was overall survival. Statistical analysis was done by both intention to treat and per-protocol. 5 year event rates were collected and survival curves were used to determine their 95% confidence intervals. The Kaplan-Meier method was used to plot survival and the log-rank test was used to analyze the differences in survival between the two groups, as well as between the group that received ELIOT according to the clinicopathological characteristics of breast cancer. Hazard ratios were obtained for IBTR and deaths for intraoperative radiotherapy and external radiotherapy. Multivariable Cox proportional hazards regression was used to identify independent factors associated with IBTR among patients who received intraoperative therapy.

Study Results

Outcomes were assessed 5 years from the end of the accrual. In the intraoperative radiotherapy group, there were 35 occurrences of IBTR, yielding a 5 year event rate of 4.4%, which is within the prespecified equivalence margin of 7.5%. Although this result falls within the equivalence margin, it is significantly greater than the 5 year event rate in the external radiotherapy group, which was 0.4%. The hazard risk for the development of IBRT was 9.3 for patients assigned to the intraoperative radiotherapy compared with those assigned to external radiotherapy. The 5-year occurrence of true local relapse was also significantly higher in the intraoperative radiotherapy (2.5%) compared to the external radiotherapy group (0.4%). A

second ipsilateral breast carcinoma occurred in 1.9% of the intraoperative radiotherapy group but did not occur in any patients who received external radiotherapy.

The 5 year event rate of regional lymph node metastasis was significantly higher in the intraoperative radiotherapy group (1.0%) compared to the external radiotherapy group (0.3%). A higher percentage of patients in the external radiotherapy group (1.7%) developed contralateral breast cancer compared to 1.1% in the intraoperative radiotherapy group. The development of distant metastasis was the same in both groups. When comparing the intraoperative radiotherapy group to the control, there was no significant difference in the development of primary cancer in other sites. Overall survival at 5 years was about the same in both groups with 96.8% survival in the intraoperative radiotherapy group and 96.9% in the external radiotherapy group. There was also no significant difference in the number of deaths from breast cancer in the two groups or the number of deaths attributable to other causes. The per-protocol analysis resulted in similar findings for all outcomes. Data on the side effects from radiotherapy was not available for all patients.

In summary, intraoperative radiotherapy with electrons resulted in significantly higher local recurrence and new ipsilateral breast tumors compared to the standard postoperative external radiotherapy. There was no difference in overall survival at 5 years between the two groups.

Study Critique

This is a randomized control trial so the chance of selection bias is low. However, tha absence of blinding or masking leaves the possibility of confirmation bias. The main analysis in this study was done by intention to treat, which while more realistic given patient noncompliance, makes it difficult to determine the true efficacy. It would be best to have analysis both per protocol and intention to treat in order to increase confidence in study results. The experimental and control groups were close to equal in number, with 601 in the external radiation group and 585 in the IORT group. A larger number of participants in each group would also lead to more trustworthy results. The study had some issues with recording information on side-effects from the radiotherapy modalities, however, our research will focus on recurrence rates and therefore this information is not crucial.

Study #3

Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial (8).

Objective: Compare 5-year local recurrence results of single-dose targeted intraoperative radiotherapy (TARGIT) versus fractionated external beam radiotherapy (EBRT) in treatment of breast cancer.

Study Design

The TARGIT study was done in 11 countries at 33 different centers, from March 24, 2000, to June 25, 2012. It was a randomized, non-inferiority trial that enrolled 3451 patients. Participants were women aged 45 years and older that had been diagnosed with unifocal invasive ductal

carcinoma suitable for wide local excision. Patients gave informed consent, and the protocol was approved by regulatory and ethics authorities at each center prior to enrollment.

The women were randomly assigned in a 1:1 ratio to receive TARGIT or whole-breast EBRT either before or after lumpectomy. 1721 patients were randomized to the TARGIT group and 1730 to the EBRT group. The trial was risk-adapted, meaning that some participants in the TARGIT group were given supplemental EBRT if unforeseen adverse features were detected on final pathology. This was necessary in 15.2% (239 of 1571). However, this was expected in 15% of patients and was incorporated into the power calculations before the study began. Intention to treat protocol was used for all analyses. The primary outcome was absolute difference in local recurrence in the conserved breast. The non-inferiority margin was set ahead of the study at 2.5% at 5 years.

The technique of intraoperative radiotherapy (IORT) outlined in the TARGIT trial involved one dose of 20 Gy to the tumor bed, delivered by placing a spherical applicator within the breast after completion of lumpectomy. Purse string sutures were employed to ensure maximum contact between the tumor bed and the radiotherapy applicator while preserving the skin and deeper tissues.

The non-inferiority statistic was analyzed by calculating the difference in binomial proportions of local recurrences between the two randomized groups. The Z score and $p_{non\text{-}inferiority}$ were calculated using established methods. The issue of follow-up was addressed by charting absolute differences in the 5-year Kaplan-Meier estimates of local recurrence. Patients were deemed to have adequate follow-up if they had at least 5 years of follow-up or if they were seen within the year before the database lock (June 1, 2012). To compare differences between survival function and calculate p values, a log rank test was employed, with significance level set at $p<0.01$ for local recurrence.

The study also investigated whether the timing of TARGIT in relation to lumpectomy affected recurrence rates, as well as an initial analysis of overall survival; however, those topics fall outside the scope of this review.

Study Results

93.7% (3234 of 3451) of patients met the follow-up criteria as stated prior: seen within the year before data lock and/or had at least 5 years of follow-up. Of all 3451 patients, the median follow-up was 2 years and 5 months. 2020 patients had a median follow up of 4 years, and 1222 patients had a median follow-up of 5 years.

TARGIT treatment concurrently with lumpectomy was shown to be very similar to EBRT in terms of 5-year local recurrence rates: 2.1% (1.1-4.2) with TARGIT versus 1.1% (0.5-2.5; $p=0.31$) with EBRT. Put simply, there were 4 more local recurrences in the TARGIT group than the EBRT group, meaning the absolute difference in local recurrence between the two groups was within the non-inferiority margins set prior to the study (as mentioned above).

Thus, when TARGIT was delivered concurrently with lumpectomy, analysis confirmed non-inferiority to EBRT in risk of local recurrence at 5 year follow-up. The authors stated that non-inferiority was established by use of Z score and $p_{non\text{-}inferiority}$ for the outcome of local cancer recurrence.

The authors' conclusion is that TARGIT concurrent with lumpectomy within a risk-adapted approach should be considered as an option for eligible patients with breast cancer as an alternative to postoperative EBRT.

Study Critique

Patients in the TARGIT group received supplemental EBRT if unforeseen adverse features were detected on final pathology. This was necessary in 15.2% (239 of 1571), and was expected in 15% of patients, so was incorporated into the initial power calculations. However, all analyses were done by intention to treat, so interpretation can be difficult if, like seen here, large numbers of subjects cross over to other treatment. The authors claim, though, that the additional treatment of EBRT in select TARGIT group patients is not a crossover or protocol deviation, since it was required as part of the initial protocol.

Somewhat interestingly, comorbidity data was not collected prior to randomization, but the authors posit that the trial size (n=3451) is large enough that the likelihood of substantial imbalance in comorbidities between the two randomized groups is low.

Further, the study was funded by the same university that pioneered the concept and the TARGIT technique. However, as stated in the article, the funders had no role in data collection, analysis, or interpretation, nor in study design or report writing.

There was also no stated attempt to blind the patients; all the women were aware whether they were having intraoperative radiotherapy or attending daily external breast radiotherapy for multiple weeks.

DISCUSSION

Breast cancer is a common disease that affects about 13% of women in the United States, 2.6% of whom will not survive. The traditional therapy of lumpectomy followed by EBRT can be a long, difficult process for patients and their families. EBRT also carries the risk of side effects including damage to skin, muscles, and organs in the area receiving radiation, as well as long-term risks such as pulmonary fibrosis or secondary malignancy. IORT is an alternative, convenient option that localizes the radiation to the tumor bed, therefore decreasing significant side effects of treatment. There is currently limited research involving the effectiveness and safety of IORT. The goal of this review is to determine if IORT is non-inferior to EBRT in relation to 5 year local recurrence rates. An overview of the recurrence rates from the three studies analyzed is shown below in table 3.

Study	IORT 5 year local recurrence rate	EBRT 5 year local recurrence rate
Cedolini (2014)	0.8%	0.8%
Veronesi (2013)	2.5%	0.4%
Vaidya (2014)	2.1%	1.1%

Table 3: 5 year local recurrence rates of IORT versus EBRT

Study 1 results indicate that no significant difference was detected in the 5 year local recurrence rates between the group that received IBRT and the group that received EBRT. Although the main focus of the review is to examine local recurrence rate, it is important to note that there was no significant difference in survival rates and IBRT was shown to elicit fewer skin and chest complications compared to EBRT. The small size of this study and the unequal number of participants in the experimental and control groups, have led us to consider these results as less valid compared to the other two studies in our review.

Conflicting results were found in study 2, where IORT 5 year local recurrence rates were significantly higher than EBRT 5 year local recurrence rates by 1.1%. However, when analyzing ipsilateral breast tumor recurrence rates, as opposed to strictly local recurrences, there was no significant difference between the two groups. Like study 1, study 2 also showed no statistical difference in overall survival.

Analysis of study 3 confirmed non-inferiority to EBRT in 5 year local recurrence risk. This is not to say that there was no difference between the recurrence rate - just that the difference fell within the non-inferiority margin that was set ahead of the study at 2.5%. The difference of 1% as seen in table 3 is not inconsequential and should be disclosed to patients considering this treatment. The authors of this study concluded that IORT should be considered as an option for eligible patients as an alternative to postoperative EBRT.

When compiling the results of 5 year local recurrence rates from the three studies above, we cannot conclude with absolute confidence that IORT is non-inferior to EBRT. It seems as though the risk of local recurrence may be slightly higher with IORT, but this difference was found to be statistically significant in study 2 and not statistically significant in study 3. More studies are needed to measure the risk of local recurrence in order to provide patients with informed decision making. Although the risk may be deemed statistically significant, it may not be considered clinically significant if the patient is opposed to undergoing EBRT due to the inconvenience and various complications.

CONCLUSION

For women over age 40 with breast cancer, does IORT demonstrate non inferiority based on rates of local tumor recurrence within 5 years compared to traditional EBRT?

Intraoperative radiotherapy is a convenient, relatively quick treatment with a favorable side effect profile when compared to external breast radiotherapy. Further studies should be done to

confirm the non-inferiority of IORT based on 5 year local recurrence rates. However, the significant benefits of IORT, including convenience and minimization of side effects, make it a reasonable alternative to EBRT. If studies continue to prove non-inferiority, IORT could become standard of care for breast cancer patients post-lumpectomy.

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