Radiol Oncol 2001; 35(1): 35-41.

Intraoperative radiation therapy (IORT) to the tumor bed only for breast cancer: technique and outcome

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Background. *Recent published reports have demonstrated that not all patients with early stage breast cancer need the entire breast irradiated for local control of their disease. To address the difficulties of several weeks of irradiation treatment, investigators have utilized different radiation techniques and treatment schedules that reduce the overall treatment time without compromising outcome.*

Patients and methods. *An analysis was made of 7 patients treated on protocol with local intraoperative radiation (IORT) alone to the lumpectomy site after surgery with or without axillary dissection. All patients received IORT with 120 kV x-rays to the tumor bed at the time of resection. Doses ranged from 1500 cGy to 2000 cGy. Three patients were stage I, two stage IIA, and two stage IIB.*

Results. *With a mean follow up of 123 months (range 86 to 139 months), two of seven patients developed a local recurrence which were treated with mastectomy. The disease specific survival is 100% and overall survival is 86% with one patient being dead without disease. The cosmetic outcome of the 5 patients with their treated breast remaining have expressed satisfaction with the results. No treatment related complications have occurred.*

Conclusions. *The results of our pilot study support the findings that not all patients with early stage breast cancer need the entire breast irradiated for durable local control of their disease. However, patient numbers in this study are low and any conclusions need further evaluation with larger trials.*

Key words: breast neoplasms-radiotherapy; intraoperative radiation, breast cancer, breast conservation therapy

Received 25 September 2000
Accepted 4 October 2000

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Introduction

Breast conserving therapy (BCT) is a well established mode of treating early stage breast cancer. Several prospective randomized studies have demonstrated equivalent efficacy in overall and disease-free survival in patients undergoing either BCT or mastectomy.[1-8]

Furthermore, BCT eliminates the emotional and psychological stress associated with removal of the breast. Currently, standard radiation treatment after lumpectomy involves treating the entire breast with external beam irradiation often followed by a local boost to the tumor bed. The rationale for the boost is that most recurrences involve the tumor site or near it.[9,10] Radiation treatment generally involves 6-7 weeks of once-a-day treatment. The difficulties to patients with such lengthy treatment involve transportation issues, employment issues and physical limitations of the patient. These difficulties may be a major reason why many eligible patients for BCT do not receive it.

These factors have led to the hypothesis that radiation alone to the primary tumor bed may be enough for local control of disease with BCT. We report here on the long-term outcome of seven patients treated on a pilot study at Roswell Park Cancer Institute for their breast cancer with local radiation alone using intraoperative irradiation (IORT) to the tumor bed after lumpectomy with or without axillary dissection.

Patients and methods

Seven patients with breast carcinomas were treated with adjuvant radiation using IORT alone to the surgical bed after lumpectomy with or without axillary dissection.

Patients were assessed for age, race, menopausal status, family history, T-stage, nodal status, hormone receptor status, margin status, and grade. Details of patient and tumor characteristics are outlined in Tables 1 and 2.

The mean age of the patients treated was 58 years (range 43-70 years). Six of the seven patients were Caucasian and one patient was Hispanic. Two of the seven were premenopausal defined by cessation of menses at the time of treatment. Two patients had a positive family history of breast cancer with having one or more members of the immediate family diagnosed with breast cancer.

Patients were staged according to the American Joint Committee on Cancer (AJCC). Three patients had stage I and four stage II disease. Tumor staging include T1c (3), T1b (1), T2 (2), and T3 (1). Axillary nodal status was assessed in six of seven patients. One patient did not have the axilla surgically assessed because of medical reasons and was clinically negative. Four of the six were node negative and two were positive, one with 4/37 nodes positive and one with 3/13 nodes positive. Five of seven patients were hormone receptor positive. Margins were negative in all patients.

All of the patients had serial post-treatment mammograms at Roswell Park Cancer Institute (RPCI). These were reviewed in-house with specific attention to any alteration of the appearance of the surgical excision site or changes associated with whole breast irradiation (*i.e.*, increased parenchymal density and/or skin thickening).[11]

All patients were treated with intraoperative radiation using orthovoltage 120 kVp x-rays to the tumor bed at the time of resection. A Picker Zephyr 120 machine was rebuilt into a compact portable unit for use in a designated operating suite. The applicator size and prescribed dose were selected at the time of surgery following lumpectomy with or without axillary node dissection. Five of the seven patients received a dose of 1500 cGy to the tumor bed and two patients received 2000 cGy.

All patients have been followed closely since completion of treatment with physical examinations, mammograms, chest x-rays, and standard laboratory studies. Cosmetics has been assessed by both the patient and physician by expression of either satisfaction or dissatisfaction with the appearance of their breast. This included shape and texture of the breast as well as the skin color.

A retrospective review of the medical records was made to determine treatment

Table 1. Patient characteristics

Patient	Age	Race	Stage	Menopausal Status	Fm Hx	Birth Control Use
1	70	Caucasian	IIA (T1cN1)	Post	no	no
2	43	Caucasian	IIA (T2N0)	Pre	yes	no
3	51	Caucasian	I (T1cN0)	Pre	no	no
4	62	Hispanic	IIB (T2N1)	Post	no	no
5	56	Caucasian	I (T1bN0)	Post	no	no
6	63	Caucasian	I (T1bN0)	Post	no	no
7	60	Caucasian	IIB (T3N0)	Post	yes	no

Fm Hx = positive family history of breast cancer

Table 2. Tumor characteristics

Patient	Pathology	Quadrant	Margins	Grading	T Stage	Nodal Status	ECE	ER/PR
1	IDC	UOQ	(-)	high	Tic	pN1(4/37)	(+)	(+)/(+)
2	IDC	UIQ	(-)	high	T2	pN0(0/9)	(-)	(+)/(-)
3	IDC	LOQ	(-)*	high	T1c	pN0(0/29)	(-)	(+)/(-)
4	IDC	UOQ	(-)	high	T2	pN1(3/13)	(-)	(-)/(-)
5	IDC	UOQ	(-)	inter	T1c	pN0(0/15)	(-)	(-)/(-)
6	IDC	UOQ	(-)	high	T1b	pN0(0/25)	(-)	(+)/(+)
7	ILC	UOQ	(-)	inter	T3	not assessed	(-)	(+)/(+)

* Close: < 2 mm

IDC = Invasive ductal carcinoma; ILC = Invasive lobular carcinoma; UOQ = upper-outer quadrant; UIQ = upper-inner quadrant; LOQ = lower-outer quadrant; ECE = Extra capsular extension; ER/PR = estrogen and progesterone receptors

rendered and the events of local control, distant failure, disease-specific survival, overall survival, cosmetic outcome, and complications (Table 3).

Results

Serial post-treatment mammograms were available for review on each patient and showed no alteration of the post-excision mammographic appearance for a median follow-up of 6 years (range 2-10 years). Five of 7 (71%) patients had mammographic evidence of post-surgical scarring consisting of architectural distortion and focal skin thickening. There was no short or long-term alteration of the appearance of the primary excision site after intraoperative radiation treatment. There was no identifiable skin thickening or increased mammographic parenchymal density attributable to IORT.

After a mean follow-up of 123 months (range of 86 to 139 months), 6 of 7 patients were free of disease. Two of seven patients recurred locally. One patient with stage I, T1cN0M0 recurred in the surgical scar 36 months after local treatment, while the second patient with local recurrence, stage IIB, T2N1, recurred within the treatment bed at 120 months. These patients both underwent mastectomy and remain disease-free 70 months later and 12 months respectively. Therefore, the disease-specific survival is 100%. One patient died of other causes without evidence of disease. Regarding cosmetic outcome, the 5 patients who have successfully preserved their affected breast have expressed personal satisfaction with the results, as had the two patients with local failures up

Table 3. Treatment given and outcome

Patient	Surgery	TAM	Surface Dose	Follow Up (month)	Local Failure	Distant Failure	Status
1	Lump + Ax	+	1500 cGy	139	no	no	ANED
2	Lump + Ax	-	1500 cGy	132	no	no	ANED
3	Lump + Ax	+	1500 cGy	133	yes	no	ANED
4	Lump + Ax	+	1500 cGy	135	yes	no	ANED
5	Lump + Ax	-	2000 cGy	137	no	no	ANED
6	Lump + Ax	+	2000 cGy	132	no	no	ANED
7	Lump	+	1500 cGy	86	no	no	DNED

TAM = tamoxifen; Lump = lumpectomy; Ax = axillary dissection; ANED = alive, no evidence of disease; DNED = died of other causes, no evidence of disease

until the time of their mastectomy. No treatment related complications have occurred.

Discussion

To address the difficulties of several weeks of irradiation treatment, investigators have utilized different radiation techniques and treatment schedules that reduce the overall treatment time without compromising outcome. By reducing the overall treatment time, many patients could potentially be able to receive BCT who might not otherwise because of difficulties related to a several week course of radiation. One technique employs the use of hypofractionated external beam radiation treatment (EBRT) of the entire breast with the number of treatments reduced by delivering higher doses per fraction.[12] Another technique combines whole breast EBRT with intraoperative electrons to boost the surgical bed, thereby reducing the number of boost treatments by giving only one treatment at the time of surgery.[13] In addition to different techniques and treatment schedules to reduce the overall treatment time, the possibility of treating only the tumor bed and not the entire breast is currently under investigation.

The rationale for giving only local irradiation to the tumor bed region is supported by both pathologic data from mastectomy specimens and patients treated with tumorectomy alone that has shown a relatively low risk of tumor burden and failure rate distant from the primary tumor site. In evaluating over 200 mastectomy specimens, Holland *et al.* found 32% of patients with extensive intraductal component (EIC) and only 12% of patients without EIC had residual disease greater than 4 cm from the cancer removed by surgery.[14] In another report as high as 36% of mastectomy specimens had either in-situ disease or invasive disease between 2 and 4 cm from the tumor site.[15]

In addition several reports of patients treated with local surgery alone have identified subsets of patients that have the tumor bed quadrant as the predominate site of recurrence and are consequently at a very low risk of recurrence elsewhere within the breast. Fisher *et al.* found that of 1108 pathologically patients able to be evaluated and treated with lumpectomy (9.9%) from the NSABP protocol 6, 110 patients developed a local breast recurrence. All 110 patients had their recurrence within or close to the quadrant of the initial or index cancer.[9] In another series, Liljegren *et al.* had 33/36 (77%) of all local recurrences within the surgical field after wide excision alone.[10]

Since the risk of recurrence appears to be low outside a margin around the surgical resection, can irradiation of the surgical bed achieve the same local control as irradiating the entire breast with a boost to the tumor

bed? The use of local irradiation alone to the surgical bed with radioactive implants or IORT electrons would significantly reduce the number of treatments that patients would receive from several weeks of once-a-day treatment to only a single day of treatment. The use of IORT with electrons is not a new concept with its benefits having been reported for solid tumors, most notably for intraabdominal or pelvic tumors;[16,17] however, its use in breast cancer, however, has mainly been limited to boosting after external beam radiation treatment (EBRT) to the entire breast.[14]

Furthermore, IORT with orthovoltage has been successfully utilized for other sites including the treatment of rectal, gynecologic, and pancreatic malignancies.[18-20] In our series, orthovoltage was selected over the use of electrons at the time because of difficulties with transporting the patient to the radiation department where electrons could be delivered. Other advantages of using the 120 kVp machine included low cost, ease of radiation protection, and direct observation of the patient 5 ft away from the anesthetist with immediate access to the patient if needed. Disadvantages of the system included a shallow fall-off of dose, and a relatively low output of 100 cGy per minute. Orthovoltage x-ray beams can potentially offer a simple, generally applicable, alternative treatment modality for intraoperative radiotherapy. The limited choice of x-ray energy, however, requires that a compromise be made between providing an adequate depth of penetration to cover the tumor volume while minimizing the dose to underlying tissues.

The use of local irradiation alone after tumorectomy in early stage breast cancer is currently being explored in subsets of patients felt to be at low risk for a recurrence outside of the surgical bed. Recent reports using brachytherapy alone to the tumor bed have encouraging results. Perera *et al.* reported only 1 infield recurrence out of 39 patients treated with high dose rate brachytherapy (HDR) to the primary tumor bed at a median time of 20 months.[21] Similarly a pilot study using low dose rate brachytherapy (LDR) by Vincini *et al.* demonstrated no local recurrences for 51 women at a median of 20 months follow-up. Selection criteria required tumors to be 3 cm or less, margins greater than or equal to 2 mm, no extensive intraductal component (EIC), a level I and II axillary dissection with up to 3 lymph nodes positive, pre- and post-operative mammograms, breast technically suitable for implant, implant performed within 8 weeks of last breast surgery, and patients at least 40 years of age.[22]

Additionally, Kuske *et al.* have had no local breast recurrences involving 51 patients treated with either LDR or HDR brachytherapy with a four year median follow-up. Cosmetics was good to excellent in 78% treated with LDR and 67% for HDR.[23] The Guy's Hospital experience using local LDR brachytherapy reports only two isolated local regional recurrences (7.5%) and a 96% good to excellent outcome.[24] In contrast, Ribeiro *et al.* had inferior results when local radiation to the involved quadrant using 10 MeV electrons was utilized vs treating the entire breast with tangent fields. At six years follow-up, both axillary and breast reccurrence were higher for the local radiation treatment arm. A 20% recurrence rate in the breast for lobular carcinomas in the quadrant - radiation arm was felt to contribute to this difference.[25] A current phase II Radiation Therapy Oncology Group (RTOG) trial is ongoing comparing low dose rate (LDR) with 45Gy vs high dose rate (HDR) with 34 Gy brachytherapy in patients meeting criteria for low risk for recurrence outside of the surgical bed.

Our observation that intraoperative radiation treatment does not alter the mammographic appearance of the primary excision site is important because a majority of early local recurrences after breast-conserving therapies occur at or near the primary exci-

sion site. Stability or resolution of the mammographic post-surgical changes on serial mammograms is an essential component of the mammographic analysis in the follow-up of these patients.[11] The lack of any appreciable mammographic changes often associated with whole breast irradiation may improve the sensitivity for detection of recurrence for some patients.

Our study and the brachytherapy studies suggest that tumor bed irradiation alone can be effective in controlling disease within the breast for selected early-stage patients and provide good to excellent cosmetics as judged by both patient and physician. In our series, despite not all of the patients fitting the strict criteria of more modern studies exploring the use local radiation alone (*e.g.*, no lobular histologies, no tumors larger than 3 cm, no associated extensive intraductal component), five of seven have achieved local control with the two local failures occurring at very long intervals after treatment (Table 3).

The optimal treatment for breast cancer patients desiring breast preservation is in evolution. In our pilot study, two patients have failed locally within the treatment site at long intervals from treatment, which indicates that patients may require lifetime follow-up and perhaps higher local doses to the local field than were given in this study. The benefits of treating locally with IORT with one treatment include more convenience to the patient, lower treatment costs, and less volume of normal tissue irradiated. Our results would seem to suggest that not all patients with breast cancer need the entire breast irradiated to obtain local control of their disease. However, patient numbers in this study are low and any conclusions need further evaluation with larger patient numbers using prospective studies.

Acknowledgements

We would like to thank S Kishel, R. Russo, RTT and F Wojtas, RTT, RN for the excellent patient care given to these patients and for technical support in their treatment. Also we are grateful to Dr. Remedios B. Penetrante for review of the pathologic specimens.

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