

Radiation Therapy in Breast Cancer

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Abstract : Radiation therapy has an important role as an adjuvant modality in management of breast cancer with improvement in the local control and thus quality of life of the patients. It is unclear with the existing data whether this translates to a higher survival in these patients, although recent studies suggest a trend in this direction. In addition, radiation therapy is useful in producing palliation of symptoms due to local and systemic disease in patients with advanced stages of breast cancer and recurrent disease.

Keywords: Radiation, carcinoma-in-situ, invasive breast cancer.

Introduction

Breast cancer is a systemic disease with a quarter of patients in early stage disease showing micro metastasis in bone marrow^{1,2}. The treatment of breast cancer essentially should include the treatment of local disease with surgery, radiation therapy, or both, and the treatment of systemic disease with cytotoxic chemotherapy, endocrine therapy, biologic therapy or combinations of these.

The need for and selection of various local or systemic therapies are based on a number of prognostic and predictive factors. These factors include tumor histology, clinical and pathologic characteristics of the primary tumor, axillary node status, tumor hormone receptor content, level of HER2/ neu expression, presence or absence of detectable metastatic disease, patient's comorbid conditions, age, and menopausal status.

This article is intended to discuss the role of radiation therapy in management of breast cancer and discussing the controversies and current status based on the guidelines from American Society of Clinical Oncology and Royal College of Radiologists^{3,4}.

For description of treatment practices, breast cancer may be divided into

- the **pure non invasive carcinomas**, which include lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS) (stage 0)
- **operable, local-regional invasive carcinoma** (clinical stage I, stage II, and some stage IIIA tumors)
- **inoperable local-regional invasive carcinoma** (clinical stage IIIB, stage IIIC, and some stage IIIA tumors)
- **metastatic or recurrent carcinoma** (stage IV).

Carcinoma-In-Situ:

Ductal carcinoma-in-situ (DCIS) describes a heterogeneous group of lesions characterized by a proliferation of presumably malignant epithelial cells within the ductal lobular system of the breast, without light microscopic evidence of invasion into the surrounding stroma. It is thought to represent a transitional stage in the development of an invasive tumor, with over 25-50% of tumors progressing to invasion, usually in the same breast⁵.

Extensive DCIS has traditionally been treated by mastectomy with survival rates approaching 100%⁶. This undoubtedly represents over treatment in a substantial number of patients and breast conservation is considered to be the desired objective for asymptomatic women with localized mammographically detected DCIS. The rate of local recurrence after limited resections in many

series has been shown to be correlated with size of lesion, adequacy of excision and histological features. Recurrences occur close to or at the site of the original tumour⁷.

Large tumour size (>2.5 cm) is associated with a higher risk of residual DCIS and a wider, less cosmetic excision may be required. Mastectomy is usually recommended for lesions over 4 cm. High nuclear grade in DCIS and the presence or absence of necrosis are thought to be the significant factors in determining local recurrence^{8,9}.

To date, no study of DCIS patients has shown a statistically significant difference in mortality when the three available treatments (mastectomy, excision alone and excision plus radiation therapy) are compared.

One randomized trial of 790 patients comparing radiotherapy versus no radiotherapy (NSABP B-07) has shown a 5 year actuarial local recurrence rate of 10% for patients given radiotherapy versus 21% for patients treated with excision alone⁷. The incidence of subsequent invasive lesions was markedly reduced in the radiotherapy arm. This led the NSABP to recommend that breast irradiation after local excision was more appropriate than lumpectomy alone. The beneficial effects were seen in the high grade lesions and in those where the margins were involved or uncertain⁹.

The fifteen year results of 268 patients from several institutions treated with excision followed by radiotherapy report an overall local recurrence rate of 19% with a 96% cause specific survival⁸. There is no apparent difference between pathological subgroups, although the median interval to local recurrence is 3 years in high grade comedo lesions as compared to 6.5 years for other lesions.

Based on these data it is recommended that the use of radiation after local excision all patients with DCIS 0.5 cm or greater in diameter will be appropriate. The use of whole breast radiation after breast conserving surgery reduces the relative risk of a local failure by approximately one half. The use of a radiation boost (by photons, brachytherapy, or electron beam) to the tumor bed is recommended to maximize local control, especially in patients 50 years of age or younger³.

For lobular carcinoma in situ (LCIS) there is no standard therapy recommended apart from careful observation and screening. Radiation therapy and mastectomy is not recommended as treatment on current evidence^{4,9}.

Operable Invasive Breast Cancer

Surgery, with or without radiotherapy, remains the mainstay in the treatment of early breast cancer. There are no long-term studies to determine whether surgery for palpable breast cancer improves

survival, but the benefits for local disease control are clear. Surgical treatment for breast cancer may consist of an excision of the tumour with surrounding normal breast tissue (breast conserving surgery) or a mastectomy.

Numerous randomized, controlled clinical trials have demonstrated no differences in overall survival or distant metastases in women with operable breast cancer treated with mastectomy compared with those receiving breast conserving surgery, both with use of adjuvant radiation therapy^{10,11}. However, breast conserving surgery with post-operative radiotherapy is associated with a higher local recurrence rate compared to mastectomy¹¹. Therefore, the potential risks must be weighed against the benefits, with a full discussion with the patient regarding her choice of treatment.

The indications for radiotherapy post-operatively will depend greatly on the surgery performed and on the pathological findings in the tissues removed. The surgery to the breast can vary from local excision, through quadrantectomy to various mastectomy options. Likewise axillary surgery can vary from full formal "level III" lymph node dissection to axillary nodal sampling or no axillary surgery at all.

Radiation therapy to the Chest Wall after Mastectomy

Radiation therapy to the chest wall after mastectomy is still a highly controversial area. The major issues centre on whether radiation therapy improves local control and survival, and which patients should be selected to receive it. Local recurrences after mastectomy remain uncontrolled in over 60% of patients despite further therapy¹². This highlights the need for more aggressive local control measures after surgery in these patients.

Many centers employ post-mastectomy chest wall radiotherapy on an individual basis, as a means of preventing local recurrence. The efficacy of radiotherapy with differences in risk of relapse has not been elucidated and the selection of patients for radiotherapy will be based largely on consensus definitions of high risk¹³. For patients with four or more positive lymph nodes it was shown in two recent randomized trials that there is reduction in breast cancer mortality of approximately one-third when adjuvant chemotherapy and radiotherapy to the chest wall and lymph nodes, when compared to adjuvant chemotherapy alone^{14,15}. In addition, there is no evidence that adjuvant chemotherapy alone given to node-positive women is effective in maintaining local control, when the risk of loco-regional recurrence is high (i.e. >4 positive axillary nodes)¹⁶. On the basis of these results and few other studies which have shown definite benefit of addition of adjuvant post operative radiation therapy, the current guidelines call for the consideration of post-mastectomy radiation therapy in patients with more than four positive lymph nodes^{3,17,18}.

In women with 1 to 3 involved axillary lymph nodes, the current guidelines recommend consideration of radiation to the chest wall and supraclavicular area after chemotherapy, with consideration also given to the inclusion of the ipsilateral internal mammary field³. In node negative patients, chest wall radiation therapy is indicated only when initial tumor size was more than 5 cm, or if there is positive or close margins (< 10 mm pathologically). In these patients consideration should be given for irradiating ipsilateral supraclavicular and internal mammary region also³.

In summary, chest wall radiation therapy after mastectomy has not been shown to improve overall survival although more recent

studies suggest a trend in this direction. But radiation therapy reduces local relapse rate and is indicated for this rationale in high risk patients.

Radiation therapy to axilla after Mastectomy:

After formal axillary clearance the local relapse rate is very low, even in the node-positive axilla. Radiation therapy is not recommended after formal axillary clearance (>10 lymph nodes harvested) as local control has been shown to be excellent with surgery alone and risk of lymphoedema is very high after radiotherapy to the dissected axilla^{4,19}.

After axillary sampling, in which four or more nodes have been harvested and found to be tumour-free, the axilla can be observed and treated definitively if recurrence is detected^{4,20}. If there are involved lymph nodes when the total number of nodes harvested is less than or equal to ten, then there is a choice between a further operation to perform formal axillary dissection or radiotherapy to the axilla. The option of a further surgical clearance is recommended; given the improved prognostic information obtained from axillary dissection, the lower relapse rates achieved after axillary dissection.

Radiation Therapy to Internal Mammary Nodal Region after Mastectomy:

No randomized trial has addressed the benefit of internal mammary chain irradiation on survival although sub-group analysis of some studies did suggest a possible minor effect. The clinical occurrence of internal mammary relapse is so rare as to make local control an unimportant objective²¹. Since the treatment of the internal mammary lymph nodes will greatly increase cardiac dose from radiotherapy, its routine use is not recommended⁴.

Adjuvant Radiation Therapy to the Breast after surgery less than MRM

So far it has not been possible, using prognostic factors, to reliably identify a subgroup of patients that do not require postoperative radiotherapy when surgical procedure is anything less than modified radical mastectomy²². There is no evidence that radiotherapy can be safely omitted in elderly patients without incurring an increased risk of local recurrence, although limited data suggest that the benefits are greater in women under 55²³. Several clinical trials have shown that adjuvant radiotherapy to the breast is required following wide local excision, to reduce local recurrence²⁴. It is clear from these studies that regardless of the degree of limited surgery, there is a significant reduction in recurrence rate with the addition of radiotherapy.

Current consensus calls for adjuvant radiotherapy to be an integral part of breast conserving protocols.^{3,4}

In breast conserving therapy with lumpectomy and radiation therapy, the data is inadequate to support the use of partial breast irradiation outside the confines of a high-quality, prospective clinical trial²⁵.

In addition, the current guidelines allow for the use of breast conserving surgery (pathologically negative margin required) plus tamoxifen or an aromatase inhibitor without breast irradiation in women age 70 or older with clinically negative lymph node, ER positive breast cancer based on results of two recently published studies^{3,4,26,27}.

Adjuvant Radiation Therapy to Drainage areas after limited surgeries:

The current guideline recommends regional lymph node RT in patients treated with breast-conserving surgery analogous to that recommended in patients treated with post-mastectomy regional lymph node irradiation³.

Boost Radiotherapy

The practice of boost treatments to the tumour bed after local resection and whole breast radiotherapy varies widely, reflecting the widespread uncertainty about the indications and doses required for tumour control¹³. The NSABP study has already shown that local control with radiotherapy can be achieved without boost treatment providing local excision is complete¹¹. Boost to tumor bed is currently advisable after breast conserving surgeries where tumor size >1cm or if margins are <2cm or unknown and in young patients.

Techniques of Adjuvant Radiotherapy Delivery

Radiotherapy to the breast and chest wall has evolved empirically and is commonly delivered using 25 fractions of 2 Gy each over 5 weeks. However, several simpler schedules are also used in different parts of the world, combining slightly lower doses with fewer, larger fractions with the aim of achieving the same clinical effects. Most of the radiation oncologists use schedules that are biologically equivalent to a dose of between 45 Gy and 50 Gy in 2 Gy fractions. From radiobiological principles, these schedules probably differ very little in terms of late normal-tissue effects and tumour control²⁸. However, there is now a need to compare these regimens in prospective randomized clinical trials. In the absence of further data it is recommended that 15-25 fractions may be used to treat the breast⁴.

X-rays of 4-6MV are preferred over ⁶⁰Co ³-rays for treatment of breast after breast conserving surgery, while beams of energy more than 6MV may be used during part of treatment for large pendulous breast with tangential field bridge separation >22 cm. For treatment of chest wall after mastectomy, both ⁶⁰Co ³-rays and X-rays can be used with similar outcome.

For boost, photon or electron beam or brachytherapy (HDR, LDR or mammosite) may be used. Brachytherapy yields a cosmetically poorer result, but maybe superior in patients with large breasts, tumors deeper than 4cm from the skin, microscopically positive or unknown margins, or extensive intraductal component. The preferred sequence is whole breast radiation therapy followed by boost. If axillary radiotherapy is being offered it has been suggested that daily fractionation of less than 2.5 Gy and avoidance of patient position change between breast and axillary field delivery will reduce the risk of brachial plexus neuropathy²⁹.

A recent retrospective study in node positive breast cancer patients receiving adjuvant chemotherapy showed a higher local relapse rate in the conserved breast when radiotherapy was delayed beyond four months³⁰. The Joint Council for Clinical Oncology has issued a Consensus Statement that 'in the case of early breast cancer treated by breast-conserving surgery and post-operative treatment the time interval between the two should not exceed 20 working days except for clinical reasons³¹.

The dose prescription methodology used should conform to ICRU 50 guidelines³² to allow comparison of doses in different centers. In the short term, if ICRU 50 is not adopted as the prescription

standard then the dose should be recorded to this standard after it has been prescribed to the local custom³.

Sequencing with chemotherapy

Till date, only one randomized trial has been published addressing this issue. This study randomly assigned 244 patients with stage I and II breast cancer to receive 12 weeks of postoperative chemotherapy given either before or after radiation therapy to the conserved breast. The results of this small study showed a statistically increased incidence of distant metastases in the radiotherapy first group, but there was also a trend in poorer local control in the chemotherapy first group³³. Based on the results of this study it can be recommended that if adjuvant chemotherapy is indicated, radiation therapy should preferably be given after chemotherapy is completed, unless there are factors which place patient in high risk for local recurrence.

In addition, radiation therapy may be given concurrent with chemotherapy. But current evidence suggests that methotrexate and doxorubicin should preferably be avoided during radiation therapy³.

Primary radiotherapy in breast cancer:

Whilst it is possible to achieve acceptable rates of local control using high doses (70-75 Gy) of radiation delivered by a combination of external beam and implant radiotherapy, the outcome in terms of cosmesis has been generally poor³⁴. For this reason, primary radiotherapy should only be considered when standard treatment methods have failed, or are not possible⁴.

Locally Advanced and Locally Recurrent Breast Cancer

Locally advanced disease:

Surgery is generally limited to the initial biopsy, followed by appropriate systemic therapy to bring about tumour shrinkage. Radiation therapy is used to treat locoregional disease, preceded by surgical removal of residual tumour in cases where a good initial response has occurred, whilst those patients responding poorly have a poor prognosis, and are best managed with radiotherapy in the first instance^{4,35}. Even if surgical clearance is possible after systemic therapy, initial inoperable stage is considered to have sufficient risk of local recurrence to warrant the use of chest wall (or whole breast if breast conserving surgery is done) and supraclavicular node irradiation. If internal mammary lymph nodes are involved, they should also be irradiated. In the absence of detected internal mammary node involvement, consideration may be given to including the internal mammary lymph nodes in the RT field. Treatment of axilla follows the same guidelines as that of operable breast cancer^{3,4}.

Loco-regional Recurrence after surgery and radiation therapy:

Detection of local recurrence in the conserved breast is difficult, as radiotherapy can produce changes which are difficult to interpret³⁶. Parenchymal breast recurrence is usually treated by mastectomy. Local recurrence after mastectomy is most common in the first two years and decreases with time. Many of these patients will go on to develop metastatic disease and patients should be restaged prior to local therapy³⁷. However, adequate local control is important for quality of life, as uncontrolled local recurrence is devastating, and significantly impairs quality of life. A combined approach from the breast surgeon and specialist breast oncologist is necessary for optimum results.

Isolated axillary recurrence is rare if adequate initial treatment of axilla has been carried out. Level III axillary dissection (3 % recurrence at 10 years) or prophylactic radiotherapy (8% recurrence at 10 years) at initial management are the most effective forms of prevention³⁸. If regional recurrence occurs then treatment is with further surgery or radiotherapy. In patients with axillary or internal mammary nodal recurrence and a greater than 2 year interval prior to this event, effective local salvage produces 5 year progression free survival of 25%, and a locoregional control rate of 57% at 10 years³⁹.

Metastatic Breast Cancer

Metastatic breast cancer is incurable. Once patients develop symptomatic distant metastases, the median life expectancy is two years. Modest improvements in survival from systemic therapy are generally acknowledged to occur, but there are no randomized clinical trials using control groups which did not receive chemotherapy to show this. Treatments should be aimed primarily at symptom relief and maintaining quality of life.

Despite the lack of proof of a major survival benefit, chemotherapy can be very effective in symptom palliation, and quality of life studies have confirmed this⁴⁰. Therefore all patients with metastatic breast cancer should be considered for some form of systemic therapy in form of chemotherapy or hormonal manipulation. In general, hormone therapy is used when the progression of disease is relatively slow, and a rapid clinical response is not required. Patients with oestrogen-positive tumours and those with a long disease free interval between initial surgery and relapse are most likely to respond to this therapy.

The role of radiation therapy is primarily in palliation of symptoms produced by local or systemic disease. Palliative radiotherapy can be of use in management of hemorrhagic and painful chest wall or breast lesions.

Persistent or severe localized pain from bony metastasis can be treated by radiation therapy, which is successful in over 80 % of patients. A short course of radiotherapy (1-5 fractions) is usually effective. Longer fractionation regimens are not usually required^{41,42}. Surgery may be appropriate for destructive lesions in the spine and to relieve the pain and compressive neurological symptoms of spinal instability. This should be followed by postoperative radiotherapy⁴³.

Wide-field irradiation (or hemibody irradiation) is successful for diffuse bone pain in three-quarters of patients, but is not often used in breast cancer. Radioisotope treatment with strontium has also been shown to produce benefit in 75% of patients, and is most useful in the presence of extensive blastic lesions⁴⁴.

Skull base metastases causing cranial nerve involvement necessitates prompt radiotherapy, which leads to improvement in 50-80 % of patients and is usually maintained⁴⁵.

Radiation produces general improvement in neurological function in 40-70% of patients with breast cancer with intracranial metastasis⁴⁶. Radiotherapy is the treatment of choice in patients with choroidal metastases producing benefit in 60-70% of patients⁴⁷.

Male breast cancer:

Breast cancer does occur in men, and men with breast cancer should be treated similarly to postmenopausal women, except that the use of aromatase inhibitors is ineffective without concomitant

suppression of testicular steroidogenesis⁴⁸.

Paget's disease

The management essentially depends on the presence or absence of any underlying malignancy. In patients without an advanced inoperable underlying cancer, recent data demonstrates that satisfactory local control may be achieved with breast conserving surgery including the excision with negative margins of any underlying breast cancer along with resection of the nipple areolar complex followed by whole breast radiotherapy and systemic therapy according to the extent of underlying disease^{49,50}.

Phyllodes tumors of the breast

Phyllodes tumors of the breast are rare tumors comprised of both stromal and epithelial elements. Treatment of phyllodes tumors is with local surgical excision with tumor free margins of 1 cm or greater. Lumpectomy or partial mastectomy is the preferred surgical therapy and surgical staging is unnecessary.

In those patients who experience a local recurrence, resection of the recurrence with wide tumor-free surgical margins should be performed. Local radiation therapy of the remaining breast or chest wall following resection of a local recurrence may be considered, but this recommendation is controversial⁵¹.

Lymphoma of the Breast:

The results are similar for surgery and radiation therapy in management of local disease in lymphoma of breast when combined with systemic chemotherapy. When radiation therapy is used, 45- 50 Gy is used to treat the whole breast and the lymphatic drainage areas.

Breast Cancer during Pregnancy:

Breast cancer occurring concurrent with pregnancy is an infrequent clinical event. Histologically the tumors are poorly differentiated, more frequently estrogen and progesterone receptor negative and approximately 30% are HER-2/neu positive⁵².

The management of these patients will depend on the stage of the disease, the fetal maturity and the interaction between the treatment and the pregnancy. The abdominal fetus and pelvic fetus will receive up to 2 Gy and 0.15 Gy respectively if radiation therapy of 50 Gy is delivered to chest wall of a pregnant woman even with adequate shielding. This is beyond the recommended radiation dose for fetus and so radiation therapy is contraindicated during pregnancy.

Adjuvant Ovarian Ablation

Ovarian ablation in hormone receptor positive pre menopausal patients can be carried out with low dose radiotherapy. Doses in the range of 20- 30 Gy are used over a period of 1- 2 weeks. The side effects of ovarian ablation are those of a premature menopause including vasomotor, sexual and other symptoms of estrogen depletion.

Patient Follow-up

The aims of follow-up are in general to detect recurrence at an early stage, to improve the chances that prompt treatment will influence the outcome, to screen for a new primary cancer in the same or contra lateral breast, to detect and manage treatment related toxicity especially management of treatment induced menopausal symptoms and to provide psychosocial support.

In patients who has received radiation therapy, special attention is needed to detect and manage any radiation induced late toxicities, though they are rare with modern treatment techniques and quality assurance measures. The reported late effects of radiation therapy in breast cancer includes lymphoedema of the limb, radiation pneumonitis, brachial plexopathy, rib fractures, breast/ chest wall oedema and stiffness, cardiac toxicities and very rarely, second malignancies in the irradiated tissue.

Conclusion:

To conclude, radiation therapy has an important role as an adjuvant modality in management of breast cancer with improvement in the local control and thus quality of life of the patients. It is unclear with the existing data whether this translates to a higher survival in these patients, although recent studies suggest a trend in this direction. In addition, radiation therapy is useful in producing palliation of symptoms due to local and systemic disease in patients with advanced stages of breast cancer and recurrent disease.

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