Sequencing of Therapy in Breast Cancer

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Abstract

Breast cancer represents a common malignancy in the developed world. The treatment of breast cancer is multimodal, and includes surgical management, chemotherapy, radiation, and hormonal modulation. The selection and sequencing of the different facets of treatment are based on patient and tumor variables, including prognostic scores and desire for breast conservation or reconstruction. The role of irradiation of the breast in breast-conserving surgery is well established. Radiation of the chest wall post mastectomy has also been associated with survival benefit in patients with node-positive disease. Unlike several cancers for which preoperative chemoradiation is the standard of care, radiation is generally reserved as a final step in the treatment of breast cancer, and can delay reconstruction, as the presence of an autologous flap or an implant may reduce the capacity to deliver effective chest wall radiation. The question arises therefore, if neoadjuvant radiotherapy delivered after tumor chemosensitization, but in advance of definitive surgery, might offer an advantage over adjuvant radiotherapy.

Keywords

Breast cancer, radiotherapy, immediate reconstruction, neoadjuvant, postmastectomy irradiation

Disclosure: The authors have no conflicts of interests to declare.
Received: November 5, 2013 **Accepted**: March 4, 2014 **Citation**: *Oncology & Hematology Review,* 2014;10(1):33–6 *DOI: 10.17925/OHR.2014.10.1.33*
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Breast cancer is the most common female malignancy in Europe and North America, and represents a heterogeneous group of proliferative lesions, the prognosis of which depends on a host of interrelated factors including draining axillary lymph node status, tumor size, grade, mitotic index, and molecular profile. The treatment of breast cancer is multimodal, and can include surgical management, chemotherapy, radiation, and hormonal modulation. The selection and sequencing of the different facets of treatment are based on patient and tumor variables, including prognostic scores and axillary or distant metastases.

Indications for Radiotherapy in Breast Cancer

Radiation therapy in breast cancer is indicated in all patients undergoing breast conservation, and postmastectomy in patients with T3 or T4 tumors, or with four or more positive axillary nodes.[1–4] The role of radiotherapy in breast cancer management has undergone overwhelming changes since its initial application. Its utility was highest in the pre-screening era when women often presented with advanced stage breast cancer or positive axillary disease. Technique-related cardiac complications precipitated a decline in its application, but technical improvements have facilitated its integration into standard management regimes. The aim of radiotherapy in breast cancer care is to reduce the risk for loco-regional recurrence, thereby conferring a survival advantage. Local recurrence is associated with higher rate of distant metastasis and death. Radiation of the chest wall post mastectomy has also been associated with survival benefit in patients with node-positive disease[5,6] and has been shown to greatly reduce the risk for local recurrence or chest wall failure.[5] A large review has shown that for every four local recurrences prevented, one death from breast cancer is avoided over the subsequent 15 years.[5] Postmastectomy radiotherapy also has been shown to confer a survival benefit to node-positive patients at lower risk for recurrence. The British Columbia trial showed greater relative reduction in patients with only one to three involved axillary nodes compared with those with more than four positive nodes. The role of irradiation of the breast in breast-conserving surgery is well established as it is associated with significant reduction in the rate of local recurrence as well as breast cancer deaths, by virtue of eradication of any residual microscopic disease at the surgical margins.[7] Loco-regional and distant disease-free survival benefit has been noted in patients undergoing breast conservation followed by radiotherapy,[8] and some groups therefore recommend the use of radiotherapy in the majority of patients with node-positive disease, regardless of nodal burden.[9] Postmastectomy irradiation has been shown to be particularly beneficial in patients with triple negative breast cancer, a cohort that has been previously identified as bearing an inflated risk for loco-regional recurrence irrespective of nodal status.[10]

In cases of breast cancer we tend to use chemotherapy in the neoadjuvant setting, unlike several cancers for which preoperative

chemoradiation is the standard of care, ahead of definitive surgery, with radiation reserved as a final step in treatment. This paradigm has evolved as radiation oncologists have tried to stratify patients into those requiring radiotherapy post mastectomy, based on pathologic tumor characteristics, including tumor stage and nodal status.[11] This historically applied to patients assigned to chemotherapy after mastectomy, where the pathology was easily interpretable. The equivalence of neoadjuvant chemotherapy compared with adjuvant chemotherapy in the setting of breast cancer is well established.[12] Furthermore, pathologic tumor response to neoadjuvant chemotherapy can provide important prognostic and predictive information, and can facilitate planning of further required therapeutic interventions.[13,14] The indications for neoadjuvant chemotherapy in invasive breast cancer were traditionally limited to large or locally aggressive tumors, but it is now being applied in smaller earlier stage cancer in an attempt to downsize the tumor and in some cases facilitate breast conservation.[15–17] In some institutions, the assessment of axillary nodal status is performed in advance of neoadjuvant chemotherapy.[18,19] No randomized control trials exist on investigating the role of postmastectomy irradiation in this subgroup of patients. Patients with histologic confirmation of axillary metastases prior to chemotherapy are therefore often assigned to radiotherapy irrespective of tumor or axillary response to chemotherapeutic agents. Debate remains as to how this selection process may be refined, but it remains current practice across a range of centers internationally.[5]

Role of Reconstruction in Breast Cancer Management

With improved diagnostic and therapeutic techniques, the number of breast cancer survivors is increasing, and the sequelae of treatment and their impact on quality of life are becoming a concern for patients and clinicians. Survivors of breast cancer who have undergone mastectomy can experience poor body image, low self-esteem, depression, and impaired quality of life. It is well recognized that breast reconstruction can improve psychologic health and body image in this cohort of patients. Breast reconstruction can immediately follow mastectomy, or it may be delayed, necessitating a second subsequent operation. Immediate reconstruction, as well as having superior psychologic benefits for the patient, also allows streamlining of the surgical process, requiring only one operation, thereby reducing hospital stay and cost overall.[20–24] It also allows normal breast landmarks to be preserved, facilitating shaping of a natural-appearing breast mound. For decades, immediate postmastectomy breast reconstruction was not favored in the management of breast cancer because it was felt that it could lead to increased morbidity and impaired survival by delaying adjuvant therapy. The use of immediate breast reconstruction in the group of patients who require postmastectomy irradiation is contentious—as adjuvant radiotherapy may increase the risk for capsular complications, and can have a deleterious effect on cosmesis.[20,25] While some units have used immediate breast reconstruction successfully in this subgroup of patients,[26–29] other institutions do not favor immediate breast reconstruction in patients at risk for requiring postmastectomy irradiation.[30] Delays in the administration of radiotherapy have been reported in patients undergoing immediate reconstruction.[31] Research from patients undergoing breast conservation has illustrated a correlation between increasing intervals between surgery and radiation and the risk for local recurrence,[32] and other studies have shown increased mortality risk if the interval between chemotherapy and radiation therapy exceeds 6 months.[6] Furthermore, the presence of an autologous flap or an implant may reduce the capacity to deliver effective chest wall radiation.[33,34]

Radiotherapy in the Neoadjuvant Setting

Radiation therapy delivered in advance of surgery would reduce delays between chemotherapy and radiotherapy, and similarly between surgery and radiation, and may therefore represent a favorable option. The question arises therefore, if neoadjuvant radiotherapy delivered after tumor chemosensitization, but in advance of definitive surgery, might offer an advantage over adjuvant radiotherapy. A number of large randomized phase III trials have confirmed the superiority of neoadjuvant radiotherapy over adjuvant radiotherapy in a number of other cancer sites, including rectal cancer[35,36] and extremity soft tissue sarcoma.[37,38] There are theoretical advantages in terms of timing, planning, and dosimetry. However, limited data exist on this therapeutic approach in the setting of breast cancer. Three recently completed prospective studies investigated the role of neoadjuvant radiation and taxane-based chemotherapy.[39–41] In all studies, the regimen was found to be feasible and effective. A 20-year retrospective review of patients managed with neoadjuvant chemotherapy followed by neoadjuvant radiation in a single tertiary referral center in France found the approach to be oncologically safe and to facilitate immediate breast reconstruction while avoiding delays in mandatory radiation.[42] A German study identified a survival advantage for neoadjuvant radiotherapy compared with adjuvant therapy in T2 tumors.[43] A recent prospective study showed neoadjuvant chemotherapy and radiotherapy followed by mastectomy and immediate reconstruction to be equivalent to patients assigned to delayed reconstruction following completion of mastectomy and adjuvant chemoradiotherapy in terms of oncologic safety and cosmesis.[44] These studies have been limited by small numbers and lack of standardization of chemotherapeutic regimes.

Neoadjuvant Radiotherapy Technique

One limitation in delivering chest wall irradiation in advance of surgical resection is the absence of pathologic prognostic information as regards nodal burden. Determination of exact number of nodes involved by metastatic disease, or indeed determining whether intra-thoracic nodal disease is present, is precluded by this approach. In light of this, we recommend a three-field approach to include delivery of radiotherapy to the whole breast and to the supraclavicular fossa. Computed tomography (CT) planning should be performed in advance of therapy to allow optimized targeting of therapy.

Radio-sensitization

As outlined by Siewert et al.,[45] there are numerous benefits to the delivery of radiotherapy and chemotherapy concomitantly, including organ preservation, radio-sensitization, and improved disease control. The treatment modalities exhibit 'spatial co-operation,' with radiotherapy acting to provide loco-regional control and chemotherapy against distant systemic micrometastases.[46] Concomitant application of the modalities, however, may lead to increased toxicities.[45] Sequential application of the treatments may facilitate the use of both at effective doses without increasing toxicity, and avoiding the need for dose reduction.

The most commonly applied drugs in neoadjuvant chemotherapeutic regimes include doxorubicin (Adriamycin®), paclitaxel (Taxol®), and

cyclophosphamide. Doxorubicin has been used with efficacy in the radio-sensitization of sarcoma; paclitaxel in non-small-cell lung cancer.[45] It can be hypothesized therefore that these agents could also be applied as radio-sensitizing agents in breast malignancies. Commonly used radio-sensitizing agents include cisplatin, which acts to interfere with double-stranded DNA (dsDNA) repair, and has been used with great efficacy in *BRCA-1*-associated triple negative breast cancer,[47] a particularly challenging subtype. A certain subset of triple negative breast cancers can be deemed 'basal-like' by virtue of overexpression of epidermal growth factor receptor (EGFR), c-kit, and cytokeratin 5/6. These markers potentially represent targets for radio-sensitization. Sambade et al.[48] investigated the use of lapatanib, a dual EGFR/Her2 kinase inhibitor, in combination with radiotherapy, in an *in vivo* murine model. Basal-like breast cancers exhibited complete resistance to lapatanib alone, but were shown to be highly growth impaired when radiation therapy was also applied. Similarly tumor control in Her-2 overexpressing subtypes was shown to be more pronounced when combination therapy was utilized compared with either modality in isolation. Tyrosine kinase inhibitors (TKIs), such as lapatinib, have also been shown to act in synergy with trastuzumab, and use of these agents together may further increase the efficacy of radiotherapy in Her2-positive subtypes.[49]

The luminal (hormone receptor-positive) subtypes of breast cancer have a more favorable prognosis than hormone receptor-insensitive tumors, which are associated with increased recurrence rates.[50] In a series of patients undergoing breast conservation followed by adjuvant radiotherapy, Luminal A subtypes were shown to exhibit the lowest rates of loco-regional recurrence, followed by Luminal B subtypes.[51] A Danish study also showed favorable response in hormone receptor-positive tumors to postmastectomy irradiation compared with hormone-negative subtypes.[52] It has been hypothesized that estrogen-mediated acceleration between the G1 and S phases of the cell cycle impairs DNA damage repair mechanisms in tumor cells, enhancing radiation-mediated cell death. Hormone-sensitive tumors may therefore be particularly sensitive to radiotherapy.[49,52]

Conclusion

The role of radiotherapy in breast cancer is well validated, as is the use of neoadjuvant chemotherapy to render cancers operable or to facilitate breast conservation. We propose that neoadjuvant delivery of radiotherapy will have multiple benefits from oncologic and technical perspectives, as well as from a quality of life and patient satisfaction viewpoint, without increasing toxicity to an unacceptable level. Immediate breast reconstruction is the gold standard of care for patients requiring mastectomy. As disease-free and overall survival rates from breast cancer improve, quality of life and patient satisfaction become increasingly important. Delivery of adjuvant radiotherapy can disrupt the cosmesis of the reconstruction, negating the positive psychological effect of an immediate reconstruction. The presence of a prosthesis or an autologous flap may also make radiotherapy delivery technically challenging. Irradiation of the breast prior to surgery and reconstruction can improve delivery without compromising cosmetic results. ■

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