

Regional Lymph Node Radiation Therapy in Breast Cancer

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Lymphedema (LE) after breast cancer treatment is an important long-term morbidity, resulting in functional, cosmetic, and psychological problems, all of which may significantly impact quality of life. Radiation therapy (RT) has been found to be a risk factor for the development of breast cancer-related lymphedema (BCRL) in several studies, with a predominant focus on the role of regional lymph node radiation therapy (RLNR). It is likely that an increasing number of patients in the future will receive RLNR due to the recent studies including the lack of benefit and increased morbidity of axillary lymph node dissection (ALND) in patients with positive sentinel lymph nodes and the benefits of RLNR in early-stage and locally advanced breast cancer. RLNR improves survival outcome in small a subset of patients, while exposing patients to high risk of LE. Clinicians should cautiously weigh the potential benefits of RT against the risk of LE in individual patients. In addition, clinical guideline for identifying patients at risk for LE and creating management plan for these patients are needed.

Key Words: Lymphedema • Breast cancer-related lymphedema • Breast cancer • Radiation therapy • Regional lymph node radiation therapy

INTRODUCTION

Lymphedema (LE) is a common and debilitating condition in breast cancer survivors characterized by regional swelling, typically in one or both arms [1]. Due to the increased survival of breast cancer patients, LE has emerged as an important long-term morbidity, resulting in functional, cosmetic, and psychological problems, all of which may significantly impact quality of life. Recent data from a meta-analysis suggest that more than one in five patients who survive breast cancer will develop this complication [2]. However, the reported incidence of breast cancer-related lymphedema (BCRL) after treatment varies widely, ranging from less than 5% with lumpectomy alone to more than 60% when treatment includes mastectomy with axillary lymph node dissection

(ALND) and radiation therapy (RT) [3]. Although the etiology and risk factors of BCRL are multifactorial and not fully understood, type of breast surgery, extent of axillary surgery, radiation therapy, and chemotherapy are commonly cited risk factors [4]. RT has been found to be a risk factor for the development of BCRL in several studies, with a predominant focus on the role of regional lymph node radiation therapy (RLNR) [5].

MAIN

1. Regional lymph node radiation therapy in breast cancer

RT is a critical component of the multidisciplinary management of invasive breast cancer. Patients diagnosed with early-stage invasive breast cancer may be candidates for breast conservation therapy, which includes a lumpectomy followed often by postoperative whole-breast RT which consists of tangential RT fields that target the breast tissue, including the axillary tail of the breast. In patients who have evidence of nodal involvement after ALND, RLNR is added to the supraclavicular (SC) fossa and axilla. In patients who receive whole-

► Received: October 19, 2016, ► Accepted: October 26, 2016

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breast RT only, the incidence of LE after lumpectomy plus ALND ranges from 1.8% to 10-16% [6-8]. This risk increases to 18-23% in those receiving wholebreast RT plus RLNR [7,8]. Patients with more advanced disease are often treated with mastectomy and postoperative RT is incorporated if the tumor is 5 cm or if four or more lymph nodes are involved.

The indications for treatment of the regional node basins depend on the number and location of the involved nodes. Depending on extent of disease, RT may be indicated to the axillary, SC, and/or the internal mammary nodes. Historically, most patients with breast cancer with lymph node involvement were treated to the fields that covered the SC and axilla. Dose is 46-50 Gy in 23-25 fractions to regional nodal field. In patients who have undergone complete ALND, there is generally consensus that directed RT to the axilla is unnecessary. The axilla is treated in selected patients with positive nodes, or in patients with inadequate or undissected axilla. Depending on the dose distribution and patient's anatomy, a posterior axillary boost (PAB) may be considered. It is important to individualize RT planning and delivery. CT-based treatment planning is encouraged to delineate target volumes and adjacent organ at risk.

The recent two studies, NCIC-CTG MA.20 and EORTC 22922/10925, evaluated the addition of RLNR to the internal mammary nodes and the upper axillary nodes including the SC region, in addition to whole-breast RT or chest wall irradiation after lumpectomy or mastectomy, respectively [9,10]. In MA.20, regional recurrences were reduced from 2.7% with breast irradiation only to 0.7% with the addition of RLNR [9]. An improvement in disease-free survival was seen from 77% to 82% at 10 years in those who received RNRT compared to those who did not. In EORTC 22922/10925, RNRT reduced the incidence of regional recurrences from 4.2% to 2.7% and decreased the rate of distant metastases from 19.6% to 15.9% at a median follow-up of 10.9 years [10].

2. The changing role of axillary staging and treatment

Over the past two decades, sentinel lymph node biopsy (SLNB) has been developed and replaced ALND for the staging of patients with clinically node-negative status, demonstrating significantly lower morbidity rates, while resulting in equivocal regional recurrence rates and overall survival [11,12]. With the introduction of SLNB, the removal of one or two lymph nodes rather

than a complete ALND for staging has led to a reduction in the risk of LE, with women having 3-year incidence of LE of 14% after complete ALND compared with 8% in those who only had SLNB [13]. Recent findings from several surgical trials have extended the option of omission of completion ALND in some patients with positive sentinel lymph nodes (SLNs) and offering SLNB after neoadjuvant chemotherapy (NCT) for patients with initially node-positive [14,15]. The ACOSOG Z0011 trial demonstrated no difference in the rates of regional recurrence, disease-free survival (DFS), or overall survival (OS) in patients with limited nodal involvement receiving SLNB randomized to completion ALND or no further axillary treatment [14]. In the ACOSOG Z1071 trial, among patients with biopsy-proven clinical node-positive breast cancer who had 2 or more SLNs examined, a post-NCT SLNB false negative rate was 12.6 %, which exceeded their pre-specified threshold of 10% [15]. The expanding role of SLNB alone is might lower the incidence of LE.

3. Regional lymph node radiation therapy and lymphedema

RLNR may cause LE by inducing fibrosis of axillary tissue surrounding the lymphatics, even though the lymphatics themselves tend to be radio-resistant [16]. In contrast, LNs are radio-sensitive, with post-irradiation findings of lymphocyte depletion and fibrosis in the areas of preexisting tumor.

The impact of RLNR in the development of BCRL has been confirmed in several studies. Coen et al. evaluated 727 patients treated with breast conservation therapy with or without RLNR. The rate of BCRL was 2% with tangents alone and 9% with regional nodal volumes included. RLNR found to be only significant risk factor of BCRL [17]. Hayes et al. evaluated axillary boost by examining the rates of LE in 2,579 women who received RT to the breast, breast and SC, or breast, SC, and axilla with a PAB. The LE rates were 16%, 23%, and 31%, respectively, with the addition of RLNR, obesity, chemotherapy, and the number of nodes dissected found to be predictors for the development of BCRL [8]. Warren et al. showed that the addition of RLNR, either with SC region or SC plus PAB, significantly increased the risk of LE when compared with breast or chest wall RT alone [18]. The rates of LE were 3% with tangent alone, 22% with SC, and 21% with SC plus PAB. Chandra et al. analyzed technical RT factors (SC field lateral border, type of boost, type of tangent, field

energy/fraction size/dose) associated with the development of LE, using 172 breast cancer patients who received RLNR [19]. The 2-year cumulative incidence of LE was 22% for SC and 20% for SC plus PAB. Of the RT parameters tested, none was associated with an increased risk of LE development.

4. Preventative methods

It is likely that an increasing number of patients in the future will receive RLNR due to the recent studies including the lack of benefit and increased morbidity of ALND in patients with positive SLNs [14,20] and the benefits of RLNR in early-stage and locally advanced breast cancer [10,21]. RLNR improves survival outcome in small a subset of patients, while exposing all patients to high risk of LE.

The risk of LE can vary according to type of surgery performed, as well as the size of the RT fields, the dose to normal tissues, the dose per fraction, the total dose, and the technical quality of RT treatment plan. Larger studies may be needed in understanding what components of RLNR predispose patients to the development of BCRL. In addition to improvement in the surgical techniques, RT techniques have also evolved over time and 3-dimensional treatment planning is now routinely used. Furthermore, more advanced techniques such as intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) can more precisely deliver radiation to the target area while sparing surrounding normal lymphatics [22]. It is also important Identifying in which patients RLNR can be safely omitted based on clinical and biologic factors. In addition, more frequent surveillance of arm swelling and use of proactive education and management appear to be necessary in patients at high risk for LE.

CONCLUSION

LE remains a common problem following breast cancer treatment and chronic, debilitating disease. More than one in five women who survive breast cancer will develop arm LE. The role of RLNR in the development of LE has been confirmed in multiple studies. Adoption of more advanced techniques such as IMRT and IGRT can reduce radiation dose to surrounding normal lymphatics and minimize the risk of radiation injury. Clinicians should cautiously weigh the potential benefits of RT against the risk of BCRL in individual patients. In

addition, clinical guideline for identifying patients at risk for LE and creating management plan for these patients are needed.

Conflicts of Interest

All authors declare no conflicts of interest.

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