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Radiation therapy in young women with breast cancer

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Introduction

Breast cancer is the most common cause of cancer death in women aged 20 to 59 years [1]. Younger women with breast cancer are considered a unique group of patients, among other reasons because data from epidemiological, retrospective studies indicate that young women have worse clinical outcomes, increased rates of loco-regional recurrences (LRR), and a lower overall 5-year survival [2, 3].

The fact that young women are more likely to present higher grade tumors at diagnosis than their older counterparts is partly responsible for the poorer prognosis. Young women are not screened as rigorously as older women, and the anatomical characteristics of the breast tissue for that age group makes it difficult to differentiate between normal and tumor tissue in a mammogram [4].

Intrinsic tumor characteristics also contribute to the worse prognosis in young patients. Breast cancer in young women is considered a unique biologic and oncologic entity. Tumors in younger patients (less than 40-45 years old) are frequently estrogen receptor– and progesterone receptor–negative, have an increased expression of Ki-67, human epidermal growth factor receptor-2 (HER-2/EGFR) and p53, and have greater lymphovascular invasion [4-6].

Young women are also considered to have a higher risk of developing LRR after breast-conserving surgery (BCS) than their older counterparts. Voogd et al [7] reported that women younger than age 35 had a more than nine-fold (hazard ratio: 9.24) greater risk of local recurrence after breast-conserving therapy than older women, but young women treated with mastectomy had a similar rate of chest wall recurrence compared with older patients.

On the other hand, recent evidence suggests that, although still higher than would be expected for older women, the incidence of local breast tumor recurrences and failures may be substantially lower than previously [8]. This apparent risk reduction seems to stem from several factors, including the widespread use of systemic adjuvant therapy

(endocrine and/or cytotoxic) and loco-regional treatments (surgery and/or radiotherapy) [4, 9].

Factors that significantly influence local control in young women treated with BCS include the presence of positive surgical margins, a negative lymph node status and positive family history [10, 11]. Jobsen et al [10] demonstrated that in women aged 40 years or less, the 5-year local recurrence rate was 8% in patients with negative margins and 37% in patients with positive margins. Also, the 5-year disease-free survival was 27% in patients with positive margins and 75% in those with negative margins [10].

Impact of adjuvant radiotherapy in women with breast cancer

Radiotherapy has been used for over sixty years in the treatment of breast cancer. During this time, it has been the subject of a vast number of randomized studies alone or in combination with other cancer treatments, showing that it not only improves loco-regional control of the breast tumor, but may also increase overall survival [12].

In the early years, the type of radiation therapy used for breast cancer consisted of low-voltage beams (orthovoltage) that had limited penetration and were highly absorbed by the bone compared to soft tissue. Acute skin reactions were the major dose-limiting factor, and late effects of radiation included skin necrosis, fibrosis, atrophy, ulceration, fractures, lymphedema or even the need for palliative mastectomy. In addition, local control rates were dismal [12].

Nowadays, the efficacy of radiotherapy in combination with surgery (pre- or post-surgery) for the control of subclinical disease, local control and survival, is unquestionable, and currently it is considered critical in the management of operable and locally advanced breast cancer [13]. In a trial from the Danish Breast Cancer Group including 3083 patients, adjuvant radiotherapy significantly decreased the 18-year probability of any breast cancer event from 73% in high-risk patients who did not

receive adjuvant radiotherapy to 59% in patients who received adjuvant radiotherapy. Also, in the same order, LRR rates decreased significantly from 49% to 14%, the probability of distant metastases after a LRR dropped from 35% to 6%, and the probability of distant metastases reduced from 64% to 53% [14].

Veronesi et al [15] carried out a randomized trial to compare the efficacy of radical mastectomy with that of BCS followed by adjuvant radiotherapy. Seven hundred and one women with breast cancers smaller than 2 cm in diameter were enrolled. After a median of 20 years of follow-up, they found that long-term survival rate among women who underwent BCS followed by adjuvant radiotherapy was comparable to that of women who underwent a radical mastectomy.

In early breast cancer, where variations in local treatment can considerably affect the risk of LRR and, hence, long-term survival, adjuvant radiotherapy has also been demonstrated to significantly reduce the rate of LRR from 26% to 7% in patients without and with radiotherapy, respectively [16].

Impact of adjuvant radiotherapy in young women with breast cancer

To date, there are few studies on adjuvant radiotherapy conducted exclusively in young women with breast cancer. However, this situation seems to be changing, and studies providing meaningful data are being published with increased frequency. Garg et al [17] analyzed retrospectively 107 consecutive cancer patients aged 35 years or less with stage IIA to IIIC breast cancer treated with doxorubicin-based chemotherapy and mastectomy, with or without adjuvant radiotherapy. They found that, compared with patients who did not receive adjuvant radiotherapy, patients who did had a significantly better 5-year loco-regional control rate (63% vs 88%, respectively) and 5-year overall survival rate (48% vs 67%, respectively).

More recently, Beadle et al [18], conducted a retrospective study to evaluate the impact of BCS, mastectomy alone, or mastectomy plus adjuvant radiotherapy on LRR rates in

652 patients aged 35 years or younger. After a median follow-up period of 114 months, the 10-year actuarial LRR rates in the entire cohort were 20% for BCS, 24% for mastectomy and 15% for mastectomy plus adjuvant radiotherapy. When divided according to disease stage, patients with stage I disease showed no differences in LRR rates according to the treatment strategy. However, in patients with stage II disease, the best loco-regional control rates were achieved with mastectomy plus adjuvant radiotherapy.

On the other hand, the issue of whether mastectomy followed by radiotherapy is superior to BCS followed by radiotherapy is also a matter of debate in young patients, because of the desire to achieve the best cosmetic outcome possible without risking clinical efficacy. In one of the largest meta-analyses to date, Clarke et al [16] evaluated the relationship between different local treatments (radiotherapy vs no radiotherapy; more extensive vs less extensive surgeries; and more extensive surgeries vs radiotherapy) and overall mortality in data obtained from 42000 women involved in 78 randomized treatment comparisons. Among other results, they found that BCS followed by radiotherapy yielded similar absolute gains in terms of 5-year LRR rates, 15-year breast cancer mortality risk and overall mortality as mastectomy followed by radiotherapy. Moreover, regardless of age and tumor characteristics, radiotherapy produced similar reductions in LRR rates in all major trials [16].

Impact of boost radiotherapy in young women with breast cancer

Although studies evaluating the use of boost radiotherapy have not demonstrated a significant correlation between its relative effect on loco-regional control and the patient's age, nevertheless because younger patients have an increased risk of LRR they may obtain more benefit than their older counterparts from this additional procedure [19-21]. However, to date no studies have demonstrated benefits from boost

radiotherapy regarding overall survival in patients with breast cancer, and adverse events, such as severe fibrosis, may increase significantly [20].

Complications from adjuvant radiotherapy

The last decade has brought about important improvements in the simulation, planning and delivery of radiotherapy. Acute and long-term skin, cardiac and lung toxicities have been reduced with the use of intensity-modulated radiation therapy [12]. Although more than 90% of women develop mild to moderate grade acute radiation dermatitis, and moist desquamation occurs in approximately 30% of women, the incidence of arm and breast edema has reduced to approximately 20% [12, 22]. In the long-term, fewer than 5% of women develop infection, and the cumulative incidence of myocardial infarction and coronary artery disease has decreased to 1% and less than 3%, respectively [12]. Another potential complication that may arise from the use of radiotherapy is the development of contralateral breast cancer and secondary tumors. Recent retrospective trials have shown that in women less than 40 years of age who receive more than 1.0 Grey of absorbed dose, or are irradiated with breast tangential fields, the risk of developing contralateral breast cancer may be 1.5 to 2.5-fold [23, 24] greater than unexposed women. No excess risk was observed in women older than 40 years of age. This risk increases with decreasing age, specially when there is a positive family history for breast cancer [24].

Conclusions

Evidence indicates that breast tumors in young women are a distinct biological and genetic entity. Young women have worse clinical outcomes, increased rates of LRR, and a lower overall 5-year survival than their older counterparts, characteristics that warrant the use of better preventive and therapeutic options. Currently, adjuvant radiotherapy is recommended for all women following BCT or mastectomy, because it

significantly reduces the rate of LRR and overall mortality. In addition, younger patients with breast cancer may obtain greater benefit from the use of boost radiotherapy than older patients. Nowadays, complications and adverse events resulting from the use of radiotherapy have been notably reduced, although the greater risk of developing contralateral or secondary breast cancers in younger women is still a matter of concern. Hopefully, future randomized studies will shed light on unresolved issues regarding the benefits of radiotherapy in young women with breast cancer.

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