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Review Article

Risk factors and state-of-the-art indications for boost irradiation in invasive breast carcinoma

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ABSTRACT

PURPOSE: The aim of the study was to give recommendations on patient selection criteria for the administration of boost doses after whole-breast irradiation (WBI) in invasive breast cancer based on available clinical evidence complemented by expert opinion.

METHODS AND MATERIALS: A systematic search of the PubMed database was conducted to identify factors associated with increased risk for local failure that can define risk groups, and to provide evidence for an adequate guidance to the use of the boost as a function of the risk of local recurrence in breast-conserving therapy. The authors reviewed the published clinical evidence for the use of boost after WBI, complemented by other relevant studies and, through a series of formal meetings communications, formulated the recommendations presented in this article.

RESULTS: The GEC-ESTRO Breast Cancer Working Group recommends three categories guiding patient selection for the use of a boost after WBI: (1) a low-risk group for whom boost adds little benefit, including patients aging at least 50 years with unicentric, unifocal, and clear surgical margins of at least 2 mm and no axillary lymph nodes invasion. In this group, a boost of 10−16 Gy EQD2 after WBI (25fr × 2 Gy or 15 fr × 2.67 Gy) is optional and not mandatory, (2) a high-risk group, for whom boost is considered mandatory and where dose escalation above 16 Gy EQD2 should be considered; including patients aging ≤40 years with close margins, extensive intraductal component or triple-negative phenotype, or patients with positive resection margins regardless of patient age, and (3) an intermediate-risk group, for whom the boost (10−16 Gy EQD2) is considered mandatory, includes patients below 40 years without major risk criteria, patients >40 years and <50 years regardless of any risk factors, or patients >50 years with any risk factor (close margins, tumor size >3 cm, extensive intraductal component, lymphovascular invasion, lymph node invasion, multicentric or multifocal tumors, triple-negative phenotype, or after neoadjuvant chemotherapy in case of residual tumor).

CONCLUSIONS: These recommendations may provide a clinical guidance regarding the use of boost after WBI in invasive breast cancer and holds for standard and hypofractionated WBI. Furthermore they should promote further clinical research focusing on controversial issues in the treatment of early-stage breast carcinoma.

Keywords: Breast cancer; Boost

Introduction

Over the last decades, breast-conserving surgery (BCS) followed by postoperative radiotherapy became the standard of care for the treatment of early-stage breast carcinoma (1−6). Moreover, it has been demonstrated that higher breast irradiation doses to the tumor bed

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significantly reduce the local recurrence rate (7−9). Therefore, the standard postoperative irradiation is composed of whole-breast irradiation (WBI) followed by a boost to the tumor bed.

The scope of this article is to provide an overview of the different risk factors for local relapse after BCS and to assess the role of boost delivery in different risk groups. It is beyond the scope of this article to give recommendations on target definition, delineation, or other technical issues of boost delivery. We believe that these recommendations are probably valid for different radiation alternatives for boost delivery (standard external beam radiotherapy, intraoperative radiotherapy, or brachytherapy) although the GEC-ESTRO group initially focused on multicatheter brachytherapy.

Methods and meterials

The primary goal of this report was to provide evidence to define an adequate guidance to the use of the boost as a function of the risk of local recurrence in breast-conserving therapy.

The evidence was selected and reviewed initially by one member of the GEC-ESTRO Breast Working Group and was subsequently reviewed by the other members of the group in a series of meetings for incremental systematization of the information found. Members of the GEC-ESTRO Breast Working Group have disclosed potential conflict of interest information.

A systematic literature search was carried out using the PubMed database. The search ''Breast neoplasm [MeSH]'' and ''Breast-conserving therapy [Any field]'' and ''Radiotherapy [Any field]'' yielded 2562 articles. From this initial set, 424 articles also contained the word ''boost'' in any field. This final set was reviewed manually to find the most relevant papers, according to the research question. Articles were deemed relevant if reviewing risk factors or linking recurrence patterns to either risk factors or treatment technique. This search was complemented by searches of reference lists of articles, articles found in personal files or cited in papers and reviews. A total of 281 original and review articles were retrieved and reviewed. The last search was done on January 2017.

The authors reviewed the published information on the use of a boost to the tumor bed after whole-breast irradiation (WBI) and present it in a structured style. This report has been reviewed and approved by the GEC-ESTRO breast cancer working group.

Rationale for tumor bed boost in breast cancer

Clinical rationale

Strongly supporting the concept of tumor bed irradiation are the documented failure patterns within the breast after breast-conservation treatment with both breast-conserving surgery only and breast-conserving surgery followed by whole-breast radiotherapy. Local recurrence is documented in the vicinity of the original index lesion in 67−100% of cases (10−24). In the National Surgical Adjuvant Breast and Bowel Project-06 (NSABP) trial, at a followup of 25 years, 95% of patients presenting ipsilateral breast true relapse found to develop failure at or close to the same quadrant as the index cancers (4, 13). In the EORTC ''boost vs. no boost'' trial (9), after a median followup of 5.1 years, local recurrences occurred in the primary tumor bed in 47% of the cases, 10% in the scar, and 29% outside the area of the original tumor, and 13% were diffuse throughout the breast. The reduction in ipsilateral breast tumor recurrence close to or within index quadrant in EORTC trial can be explained by the use of postoperative radiotherapy in both the arms (50 Gy to whole breast), which may be considered to treat most of microscopic subclinical disease not only in the index quadrant but also throughout the breast. This fact is clearly evident from the overall local recurrence rates in both the studies (10% in NSABP-06 and 6.2% in EORTC trial).

Elsewhere failures (any in-breast failure located beyond the area of the lumpectomy cavity), occur in only 1.5−3.5% of patients treated. Elsewhere failure rates have been documented with equal frequency in patients treated with lumpectomy only and in patients treated with lumpectomy and whole-breast radiotherapy. These findings suggest a true benefit of breast radiotherapy reducing failures in the breast tissue immediately surrounding the lumpectomy cavity (25, 26).

Pathologic rationale

The original pathologic evaluation of mastectomy specimens of patients with T1-2 breast cancers performed by Holland *et al.* (27) revealed that the specimens processed hold microscopic disease that was present in a multifocal distribution with relatively high frequency. The authors performed simulated tumor excision and residual tumor foci have been shown in high density of 1−2 cm in around 20−25% of patients/histopathologic specimens. If tumors were removed with a wide margin, the likelihood of having residual tumor foci decreased from 42% for 2 cm margin to 17% for 3 cm margin and 10% for 4 cm margin. Other authors have found multifocal foci in a large number of patients ranging from 43% to 79%, well beyond the reference tumor, being these foci the source of local recurrence (27−29). These results prove that prominent residual carcinoma is usually confined to the same quadrant as the reference tumor but can also be present elsewhere in the breast.

However, these pathologic findings correlate with clinical results, where more than two-thirds of local recurrences are located in the index quadrant. This indicates that probably, early local recurrences do not arise from these