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BOOST of radiotherapy after conservative treatment in elderly women's breast cancer: A review of the literature

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Abstract

Introduction: Breast cancer is the first female cancer in the world. The main objective of programmed radiotherapy after conservative surgery is to reduce the risk of local recurrence. Boost administered to the tumor bed has long been a subject of controversy in breast irradiation after conservative surgery, especially in elderly patients.

We carried out a literature search aimed at clarifying the role of Boost on the tumor bed in conservative treatment in patients aged over 60 years.

Methods: A review of the literature was carried out using the Pubmed, Cochrane Library, Science Direct and Google Scholar databases. The methodological quality of the studies was assessed using the Modified Sacket Scale (MSS).

Results: Through this review of the literature, based essentially on six studies presenting a high level of proof according to the MSS scale, and on the recommendations of certain learned societies, we can conclude that the Boost on the tumor bed could be "avoided" in certain patients. patients over 60 years of age even after conservative surgery (Luminal A, small size).

Conclusion: The development of gene or protein profiles that predict radiosensitivity could help select patients for radiation therapy and the dose to use.

Keywords: Age; Boost; Breast tumor; Radiotherapy

1. Introduction

Breast cancer is the first female cancer in the world. Almost all clinical studies have shown a linear increase in the incidence of this cancer with age [1].

For most women with early breast cancer, the standard treatment after conservative breast surgery is adjuvant radiation therapy and adjuvant hormonal therapy.

Radiotherapy usually consists of a prophylactic adjuvant irradiation of the remaining breast with or without lymph nodes at the dose of 50 Gy in 25 fractions (normofractionated scheme), possibly associated, according to risk factors of local recurrence, an overprint or Boost on the tumor bed at a dose of 10 to 16 Gy [2].

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The main objective of radiation therapy is to reduce the risk of homolateral breast recurrence [3].

Boost given on the tumor bed has long been a subject of controversy in breast irradiation after conservative surgery especially in elderly patients.

Given the biology of breast cancer that may be less aggressive and the increased proportion of hormone-receptor-positive tumours in this age group, the improvement of local control resulting from a higher radiation dose must be balanced against the increase in adverse effects of treatment.

In this perspective, we carried out a bibliographic research aimed at clarifying the place of Boost on the tumor bed in conservative treatment in patients over 60 years of age.

2. Material and methods

A literature review was conducted using the Pubmed, Cochrane Library, Science Direct and Google Scholar databases. The research was done using the terms breast tumor, radiotherapy, conserving surgery, boost, age, older, 60 years. We have included all articles and references that study radiation therapy and especially Boost after conservative surgery according to different age groups. The methodological quality of the studies was assessed using the Modified Sack and Scale (MSS) scale.

3. Results

We included five randomized controlled trials, the recommendations of the 15th St. Gallen Consensus Conference in March 2017, the recommendations of the NCCN 2018 scholarly society, the 2016-2017 Remagus repository and the 2019-2021 repository.

The six randomized studies had a high level of evidence on the SSM scale. The results of each study were detailed.

4. Discussion

Several studies have concluded that young patients with early stage breast cancer generally have a worse prognosis than older patients. Some identified young age as the most important prognostic factor for local recurrence [4-9].

This finding prompted the authors to investigate the role of Boost given on the tumor bed after conservative surgery and breast radiotherapy in patients in different age groups.

The EORTC study “Boost versus no Boost” attempted to answer this question in 2007 [10].

This was a Phase III randomized study with a total of 5,318 patients undergoing conservative treatment (conservative surgery followed by +/- lymph node irradiation at 50 Gy dose) between 1989 and 1996. Patients were randomly assigned to receive either a 16 Gy Boost dose on the tumor bed (2661 patients) or not receive Boost (2657 patients) with a median follow-up of 10.8 years.

The objective of this study was to study the long-term impact of a 16 Gy Boost dose on local control, skin fibrosis, and overall survival for these patients.

The median age of the patients was 55 years. The results of this study on local recurrences were in favour of Boost; the cumulative incidence of local recurrence was 6.2% for the Boost group versus 10.2% for the No Boost group ($p < 0.0001$). The number of rescue mastectomies for recurrence was reduced by 41% thanks to Boost. The OS (overall survival) at 10 years was identical for both arms (82%). Severe fibrosis at age 10 was 4.4% (acceptable) for the Boost group versus 1.6% for the Boost-free group.

The age subgroup study concluded that the incidence of local recurrences decreased with age from the age of 50 on any arm. Indeed, Boost reduced the risk of local recurrence very significantly for patients aged 40 and under (23.9% with Boost versus 13.5% without Boost) ($p=0.0014$).

Probably disappointed by the lack of impact on the SG at 10 years, the investigators repeated a new analysis of the data at 20 years [11].

Overall survival at 20 years was 59.7% in the group with Boost versus 61.1% in the group without Boost. Recurrence of the homolateral breast tumor was noted in 13% of patients without Boost versus 9% of patients with Boost (99% CI 0.52-0.81, p<0.0001). Rescue mastectomy occurred in 79% of patients in the No Boost group versus 75% in the Boost group. The cumulative incidence of severe fibrosis at age 20 was 1.8% in the No Boost group versus 5.2% in the Boost group (p<0.0001).

The age of the patients was strongly correlated with the risk of homolateral breast tumor recurrence. The cumulative incidence of tumour recurrence ranged from 34.5% (99% CI 21.9–47.2) for patients 35 years of age or younger to 11.1% (99% CI 7.6–14.6) for patients over 60 years of age.

The relative reduction of the risk of recurrence by administering a dose of Boost was significant for younger age groups (for 40 years, p=0.003; and for 41-50 years, p=0.007) but not for both older age groups (for 51-60 years, p=0.02; for age >60 years, p=0.019); the effect was not significantly different across the age group.

So, through this study, the authors concluded that an increase in radiation after whole breast irradiation has no effect on long-term overall survival, but can improve local control, with the greatest absolute benefit in young patients, although it increases the risk of severe fibrosis. The additional radiation dose can therefore be avoided in most patients over the age of 60.

Analysis of local recurrence prognostic factors in this later published study showed that for patients under 50 years of age, Boost reduced the local 20-year recurrence rate from 24% to 15% (p=0.002). For patients with CIS (carcinoma in situ), Boost reduced this rate from 22% to 14% (p<0.001). For patients under 50 with CIS, Boost reduced local 20-year recurrences by 31% to 15% (p<0.01). For patients over 60 years of age with CIS, Boost showed no significant effect (15% to 14%) [12].

Thus, while the long-term data from the “Boost versus no Boost” study have certainly shown an additional benefit for all age groups [11], it has, however, been very weak in some groups [12]. As a result, the majority of the members of the 15th St.Gallen Consensus Conference in March 2017 decided to give up Boost in those over 60 years of age with low-grade tumors, a favorable tumor biology and with an adjuvant endocrine treatment [13]. It should be noted, however, that the Boost study conducted by Bartelink et al. was based on a 1–2 cm tumour-free margin of removal and that in the presence of smaller margins of removal, a 25 Gy Boost could even take place.

In addition, according to the National Comprehensive Cancer Network (NCCN) in 2018, Boost is recommended in patients at higher risk of recurrence (people under 50 years of age with high grade or focal positive margins) [14].

In the TMF breast cancer monitoring and management framework, Remagus 2016-2017, based on international recommendations, the omission of Boost after conservative surgery with healthy banks is proposed for patients over 60 years with the presence of all these criteria [15]:

- Grade I or II
- Low or moderate proliferation
- Absence of vascular embols
- RO+ or RP+
- pN0
- Size<20mm
- Her2<0

In the 2019-2021 version of Remagus, the indication of the boost of the tumor bed is recommended in the presence of these criteria [16]:

- Age<50
- Age <60 years if triple negative and/or grade III
- Positive marges

Between July 1994 and February 1999, 636 70-year-old women followed for an infiltrating breast carcinoma classified T1N0M0 according to the TNM classification with the presence of positive hormonal receptors treated with axillary tumorectomy were randomized to receive tamoxifen plus radiotherapy (317 women) or tamoxifen alone (319 women) [17].

The main objective of this study was to determine whether there is a benefit to adjuvant radiation therapy after conservative and tamoxifen breast surgery in 70-year-old women with early stage breast cancer.

The main evaluation criteria were local or regional recurrence time, mastectomy frequency, breast cancer specific survival, time to remote metastases, and OS. The median follow-up of treated patients was 12.6 years.

At age 10, 98% of patients receiving tamoxifen by radiotherapy and 90% of those receiving tamoxifen were free of local and regional recurrences. There were no significant differences between the two groups in terms of mastectomy time, remote metastasis time, breast cancer specific survival or OS. Ten-year-old OS was 67% in the tamoxifen group with radiotherapy and 66% in the tamoxifen group. Therefore, the authors concluded that tamoxifen remains a reasonable option for 70-year-old women with early-stage breast cancer with hormonal receptor expression.

Between 2003 and 2009, 1,326 patients aged 65 years or older with early breast cancer are considered to be at low risk of recurrence (positive hormone receptors, negative axillary nodes, T1-T2 up to 3 cm maximum) who had a conservative breast and were receiving adjuvant hormone therapy, were recruited in a randomized multicentre phase 3 (76 centres and 4 countries). The objective was to assess the effect of omitting whole-breast radiotherapy on local control in elderly women at low risk for local recurrence at age 5[18].

Eligible patients were randomly assigned between radiation therapy (40-50 Gy in 15-25 fractions) (658 women) or lack of radiation therapy (668 women).

After a median follow-up of 5 years, the recurrence of the homolateral breast tumour was 1.3% in women with whole-breast radiation and 4.1% in those without radiation (p=0.0002). Overall survival at 5 years was 93.9% in both groups (p=0.34).

Authors concluded that post-operative whole breast radiotherapy after conservative breast surgery and adjuvant endocrine therapy resulted in a significant but modest reduction in local recurrence in women 65 years of age and older with a single-stage breast early cancer 5 years after randomization. However, the 5-year rate of recurrence of homolateral breast tumours is likely low enough for the omission of radiation therapy to be considered for some patients.

According to these studies, after conservative surgery and radiotherapy of the entire mammary gland, Boost in the tumor bed can be omitted in cases that meet all the following criteria for patients over or equal to 70 years of age:

- SBR I and II
- Size 3 cm
- HR (+)
- Lack of lymphatic emboli
- Lack of extensive in situ component
- Healthy margins

For patients older than or equal to 60 years of age, Boost can be omitted in the presence of all criteria raised with no lymph node invasion.

Table 1 The studies and references on which our bibliographic research was based

Study or reference	**Author**	**publication year**
Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized Boost versus no Boost EORTC 22881-10882 trial.	Bartelink H et al.	2007
European Organisation for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups. Whole-breast irradiation with or without a Boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial.	Bartelink H et al.	2015
European Organisation for Research and Treatment of Cancer, Radiation Oncology and Breast Cancer Groups. Prognostic Factors for Local Control in	Vrieling C et al.	2017

Breast Cancer After Long-term Follow-up in the EORTC Boost vs No Boost Trial: A Randomized Clinical Trial.		
De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017.	the St. Gallen International Conference	2017
Invasive Breast Cancer.	NCCN	2018
Référentiel Remagus 2016-2017	IGR	2016
Référentiel Remagus 2019-2021	IGR	2019
Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol.	Hughes KS et al.	2013
Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial.	Kunkler IH et al.	2015

5. Conclusion

Through this review of the literature based essentially on six studies and recommendations from some learned societies, we can conclude that Boost on the tumor bed could be «avoided» in some patients over 60 years of age even with conservative surgery (Luminal A, small size).

The development of gene or protein profiles that predict radiosensitivity could help select patients for radiation therapy and the dose to be used.

Two clinical trials are underway (with gene signatures): IDEA with Oncotype and PRECISION with PAM-50 to prevent irradiation in patients with low scores.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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