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A systematic review of clinical outcomes and radiotherapy-associated toxicity in multicatheter accelerated partial breast irradiation

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Abstract

Background: To integrate relevant clinical data of multicatheter accelerated partial breast irradiation (mAPBI) for reaching a comprehensive conclusion.

Methods: We did 3 meta-analyses for clinical outcomes including 1740 women from 4 articles, for acute radiotherapy (RT)-associated toxicity including 1255 patients from 5 articles, and for late RT-related toxicity involving 1565 patients from 9 papers. Clinical outcomes analyses were stratified by molecular subtypes, lymph nodes status, receptor status, and human epidermal growth factor receptor 2 (HER2) status.

Results: For the Luminal A/B phenotypes, the disease relapse and failure in survival significantly decreased when compared with triple negative (TN)/HER2-amplified subtypes ($P < .00001$). The 5-year regional nodal recurrence (RNR), 5-year distant metastasis-free survival (DMFS) and 5-year disease free-survival (DFS) of TN patients were significantly superior to HER2-overexpression patients ($P < .00001$). The 5-year cause-specific survival (CSS), 5-year DMFS and 5-year overall survival (OS) in women with lymph nodes-negative were significantly improved versus patients with lymph nodes-positive ($P = .0001$). Conversely, the positive status of HER2 compared with negative one significantly increased the rate of local recurrence (LR) ($P = .02$). For acute toxicity, the morbidity of dermatitis was significantly higher than hematoma and implant infection ($P = .01$, $P < .0001$, respectively). For late toxicity, the occurrences of fibrosis (32%) and telangiectasia (14%) were significantly higher than other complications ($P < .0001$).

Conclusion: HER2-enriched subtype compared with other subtypes has significantly increased disease relapse and failure in survival. HER2-positive status is positively associated with an increased incidence of LR. Dermatitis is the most common acute RT-related toxicity and fibrosis is the first rife late RT-related toxicity.

Abbreviations: APBI = accelerated partial breast irradiation, CSS = cause-specific survival, DFS = disease free-survival, DMFS = distant metastasis-free survival, HER2 = human epidermal growth factor receptor 2, IBTR = ipsilateral breast tumor relapse, LR = local recurrence, LRR = locoregional recurrence, mAPBI = multicatheter APBI, OS = overall survival, RNR = regional nodal recurrence, RT = radiotherapy, TN = triple negative, WBI = whole breast irradiation.

Keywords: clinical outcomes, mAPBI, RT-related toxicity, systematic review

1. Introduction

Given that the pathological data and patterns of failure indicate the residual tumor and clinical recurrence mainly limited to the tissues adjacent to the tumor-resection cavity in patients with early stage breast cancer, the notion of accelerated partial breast irradiation (APBI) is emerged as the times require.[1–8] APBI is considered as an accelerated 1-week treatment course using a dose-fractionation scheme simulated by radiobiology and suitable for eliminating the residual tumor surrounding the lumpectomy cavity.[9] This method greatly shortens the radiotherapy course and significantly decreases the required irradiation volume of mammary gland, whose tumor control and the effects of late radiotherapy (RT)-related toxicity are alike to the conventional whole breast irradiation (WBI).[10] Since these advantages of it, an increasing number of women are inclined to accept APBI instead of WBI. Thereby, several novel APBI technologies have been developed in the past few years, which can be roughly divided into 4 categories: multicatheter APBI (mAPBI), intraoperative radiotherapy with electrons, spherical balloon or metal devices, and external-beam conformal technique.[9]

The mAPBI treatment, one of the early approaches to explore the notion of APBI, has gathered most ample clinical data with

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long period follow-up and is feasible for most patients compared with other APBI techniques, but not the perfect technology for all cases.[11] Nevertheless, effective tumor control and good-to-excellent cosmetic outcomes are brought by mAPBI when appropriate knowledge and technology are available. At present, the main problems in the scientific evaluation of mAPBI as a therapeutic strategy are to demarcate and perfect its indications. To settle this issue, this article puts emphasis on investigating the clinical results by meta-analysis in the subclassifications treated with mAPBI, including molecular phenotypes, the status of hormone receptor, lymph nodes and human epidermal growth factor receptor 2 (HER2), as well as the toxicity related to RT.

2. Methods

2.1. Study design

The keywords—[(multicatheter accelerated partial breast irradiation) OR (multilumen accelerated partial breast irradiation) OR (multicatheter accelerated partial breast irradiation) OR (multilumen accelerated partial breast irradiation)]—were retrieved in the following databases-PubMed, Cochrane library, Embase and Web of Science-by 2 authors independently. The included articles were supposed to meet the following criteria: clinical studies published in English; early stage breast cancer patients treated with mAPBI; reporting the case number of clinical outcomes (survival and/or relapse) or RT-related toxicity. The exclusion criteria were involving: nonclinical trials; the study classified as review, the case report, the conference abstract and conference paper; the absence of the forementioned event count or other information that could be used to calculate the event count in the publication.

Furthermore, data were extracted from included studies and were statistically analyzed in accordance with forementioned subgroups. Generally, triple negative (TN) and HER2-over-expression diseases have poor clinical prognosis compared with Luminal A/B tumors. Therefore, we subdivided the molecular phenotype subclassification into 2 comparative cohorts, Luminal A/B subtype vs TN/HER2-enriched subtype, and TN phenotype vs HER2-enriched phenotype. Meanwhile, the remaining subgroups were analyzed in terms of status positivity vs negativity.

2.2. Statistical analysis

In this article, the clinical outcomes were mainly analyzed on 5-year disease recurrence [i.e., ipsilateral breast tumor relapse (IBTR), regional nodal recurrence (RNR), local recurrence (LR) and locoregional recurrence (LRR)] and 5-year survival [such as overall survival (OS), disease-free survival (DFS), distant metastasis-free survival (DMFS) and cause-specific survival (CSS)]. OS was defined as the time from diagnosis to death or final follow-up; the definition of DFS was the period from diagnosis to disease relapse; DMFS was calculated by the period from diagnosis to distant metastasis; CSS referred to the length of time from diagnosis to death from the cancer. The disease recurrence was calculated directly by the number of events; the incidence of failure in survival was analyzed by a postprocessing value that was computed by subtracting survival cases from total sample sizes. We scrutinized the included studies and did not find concrete number that described the association between RT-related toxicity with designed subgroups. Therefore, the comparison of their morbidity was statistically calculated by ANOVA analysis and LSD-test. These analyses were programmed via Review Manager (version 5.3) and SPSS (version 23.0).

3. Results

3.1. Article and patient characteristics

After layers of screening, which was shown in Figure 1, we finally obtained 4 articles[12–15] with 1740 women for clinical outcomes analysis, 7 trials[16–22] with 1255 people for acute RT-related toxicity analysis as well as 10 studies[16–25] with a total of 1565 patients for late RT-related toxicity analysis. Of the patients who were reported the association between molecular subtypes and clinical outcomes, 1166 (84.2%) had Luminal A/B breast cancer, 154 (11.1%) were classified into TN disease, 64 (4.6%) suffered from HER2-enriched breast tumor. A total of 861 women were collected to cover how the lymph nodes status influenced on the tumor relapse and failure in survival, in whom 72 (8.4%) had lymph nodes positivity and 789 (91.6%) had lymph nodes negativity. We gathered 140 patients with information of receptor status, of whom were assorted into following categories: 91 with positive ER status, 49 with negative ER status; 85 with positive PR status, 55 with negative PR status; 23 with HER2 positivity and 117 with HER negativity. Regarding the analysis of RT-related toxicity, we recruited 1255 women for acute toxicity and 1565 patients for late toxicity. Other details of patient characteristic had provided in Supplemental Tables 1–3 (*Appendix, page 1–2*, http://links.lww.com/MD/C801).

3.2. Clinical outcomes

For women with Luminal A/B phenotypes, the disease relapse and failure in survival were significantly decreased when compared to patients with TN and/or HER2-amplified subtypes ($P < .00001$). However, no statistical differences in 5-year LR and 5-year LRR were observed between them (Fig. 2A). Furthermore, the comparison of TN subtype vs HER2-enriched subtype showed that some clinical outcomes in former were significantly perfected ($P < .00001$), manifesting as a reduced 5-year RNR coupled with the increased 5-year DFS and DMFS (Fig. 2B).

As seen in Figure 3, there were significant improvements of the 5-year CSS, 5-year DMFS and 5-year OS in negative lymph nodes patients compared with positive status ($P = .0001$). Still, no difference of 5-year LR and LRR were detected between the 2 properties of lymph nodes.

As shown in Figure 4, the rate of LR in positive ER and positive PR had a reduced tendency by comparison with negative ones ($P = .06$, $P = .07$, respectively). Conversely, the positive HER2 status compared with negative one significantly increased the rate of LR ($P = .02$).

3.3. Radiotherapy-related toxicity

As presented in Figure 5A, the highest morbidity of acute toxicity was dermatitis, which was more frequent than hematoma and implant infection ($P = .01$, $P < .0001$, respectively), but without significant difference by comparison of breast pain ($P = .058$). In terms of late toxicity outlined in Figure 5B, the morbidity of fibrosis (32%) and telangiectasia (14%) was significantly higher than other complications, especially in seroma ($P < .0001$). The additional analyses of RT-induced adverse effect were provided in Supplemental Table 4 (*Appendix, page 3*, http://links.lww.com/MD/C801).

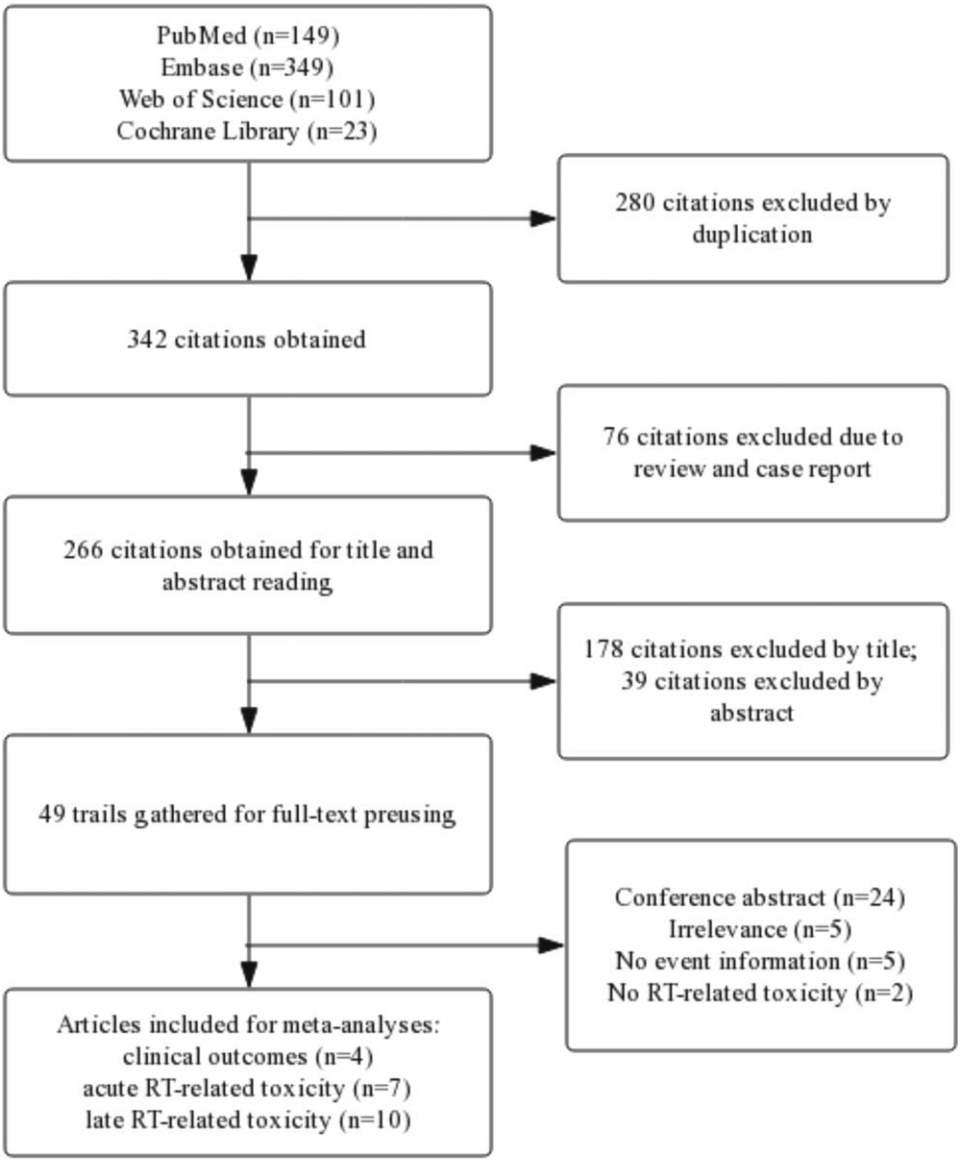

Figure 1. The flow diagram regards to the selection procedure of included articles.

4. Discussion

Several meaningful findings were presented in our study when mAPBI was utilized to treat early stage breast cancer patient. The disease recurrence and failure in survival in Luminal A/B cohort are significantly lower than TN/HER2-overexpression cohort, and in TN tumor are significantly attenuated by comparison with HER2-amplified breast cancer. Hence, the clinical outcomes of HER2-enriched breast tumor are located in the most unfavorable position. In addition, patient with negative lymph nodes significantly reduces the failure in survival when compared to patient with positive lymph nodes, despite no difference of LR and LRR between them. In the case of LR, compared to negative HER2 status, the positive one is a risk factor for significantly increasing its incidence.

APBI is a worthwhile popularizing treatment approach, which greatly shortens RT duration in comparison to WBI, and has the merit of effectively reducing the radiation exposure to breast, skin, lung, and cardiac tissue especially.[26] To our knowledge, the LR incidence and failure in survival of mAPBI are comparable to WBI, which has been demonstrated by results from 2 randomized trails (the GEC-ESTRO trail[27] and the William Beaumont Hospital group trail).[28] In the GEC-ESTRO trail, there was no significant difference between mAPBI with WBI of the cumulative rate of 5-year LR (1.38% vs 0.97%; $P=.53$) 5-year regional recurrence (0.48% vs 0.18%; $P=.39$) and 5-year DM (0.80% vs 0.93%; $P=.81$). Besides, both treatments had promising 5-year DFS ($P=.79$) and 5-year OS ($P=.11$), with no significant difference as well. Similarly, in the William Beaumont Hospital group trail, which conducted a matched-pair analysis that treated 199 patients with WBI and an identical number of women with mAPBI, no differences were shown between WBI with mAPBI in the 12-year incidences of LR (3.8% vs 5.0%, $P=.40$), regional recurrence (0% vs 1.1%, $P=.15$), DFS (87% vs 91%, $P=.30$), CSS (93% vs 95%, $P=.28$), as well as OS (78% vs 71%, $P=.06$), respectively. Moreover, they also performed a univariate analysis on mAPBI cohort, discovering that there was no association between LR with tumor size, ER status, PR status,

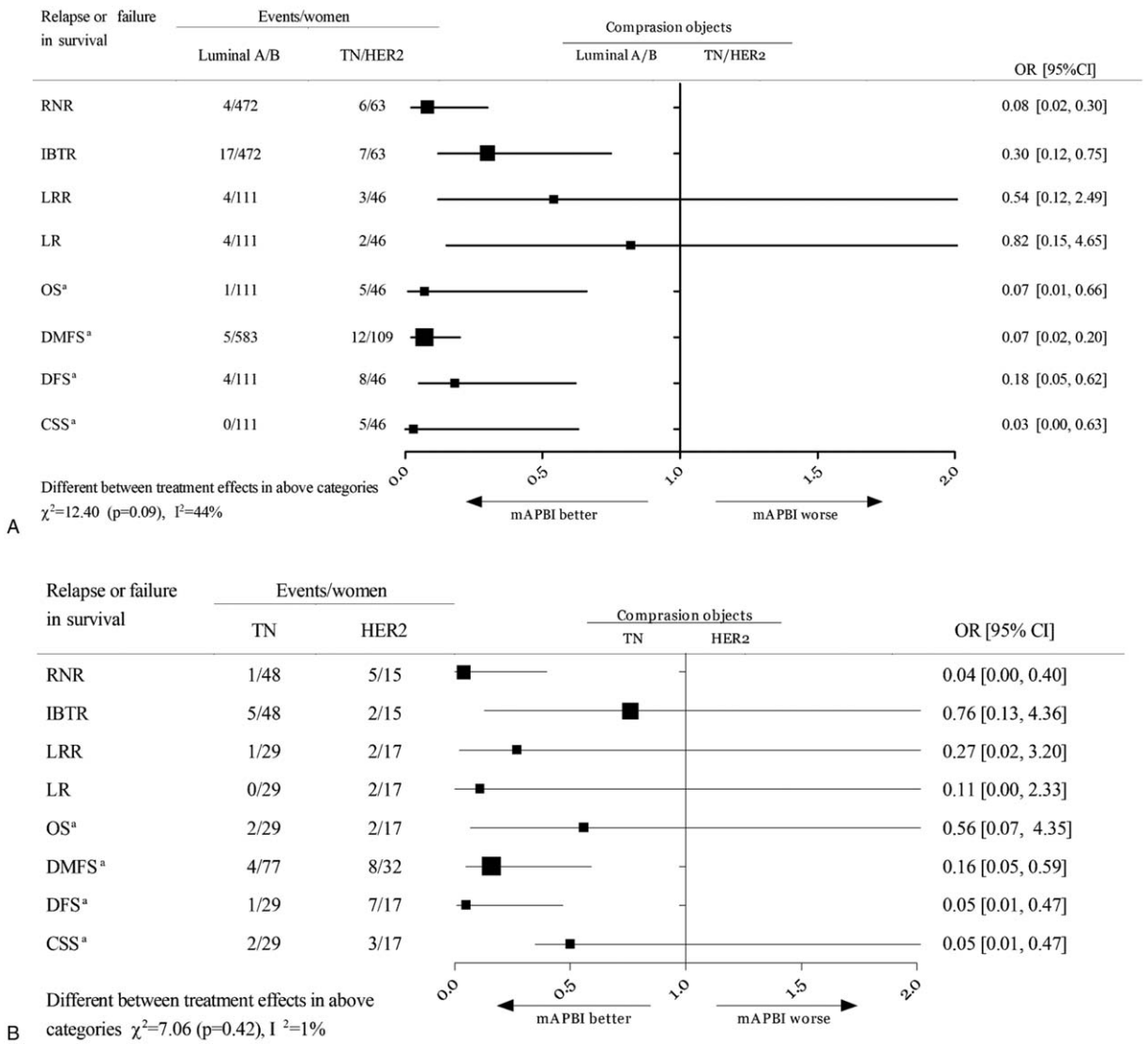

Figure 2. The comparison in molecular subtypes of disease recurrence and failure in survival. (A) Luminal A/B vs TN/HER2-enriched; (B) TN vs HER2-enriched. a: The event is the number of the failure in survival.

adjuvant chemotherapy, lymph nodes status, or margin status, which is consistent with our outcomes.

Some literatures have provided clinical results regarding the impact of molecular subtypes on early-stage breast tumor with mAPBI strategy. As analyzing the incidence of DFS, CSS, and OS, it indicated that HER2-amplifed subtype had significantly reduced them when compared with the Luminal subtypes. In the study of Anderson,[14] with a median follow-up of 5.4 years, it was showed that the 5-year IBTR incidence was 4.7% overall, 3.5% for Luminal A, 4.1% for Luminal B, 13.3% for HER2-overexpression, and 11.3% for TN subtype. Also, Luminal A subtype was in a lower risk of 5-year IBTR than other subtypes pooled (3.5% vs7.3%; $P=.02$). As for the 5-year RNR with a rate of 2.1% overall, which was 3.5% for Luminal A, 5.2% for Luminal B, 34.5% for HER2 and 11.3% for TN phenotype, it increased for patients with HER2-enriched subtype compared to other molecular subtypes pooled and for Luminal B versus Luminal A phenotype. Similarly, we have proved that HER2-expression subtype has poor clinical results, even compared with highly invasive TN subtype. Accordingly, it is believed that the clinical outcomes of early stage breast cancer women with HER2-amplified subtype locate in the inferior position when treated with mAPBI.

Up till now, the first large-scale study in regard to the effect of lymph node status on clinical outcomes of APBI in treating breast cancer was initiated by William Beaumont Hospital in 2011,[29] which enrolled 471 lymph node-negative and 39 lymph node-positive breast cancer patients. With a median follow-up of 7.8 years for node-positive status and 6.3 years for node-negative status, no significant difference was detected between them in 5-year axillary failure, DFS and OS (0% vs 0%, $P=.69$; 90.0% vs 88.0%, $P=.79$; 91.0 vs 84.0%, $P=.65$; respectively). It indicated, however, the 5-year regional relapse and distant metastasis in the node-positive women were significantly higher than node-negative women (6.1% vs 0%, $P<.001$; 8.9% vs 2.2%, $P=.005$; respectively). The CSS at 5 years showed an

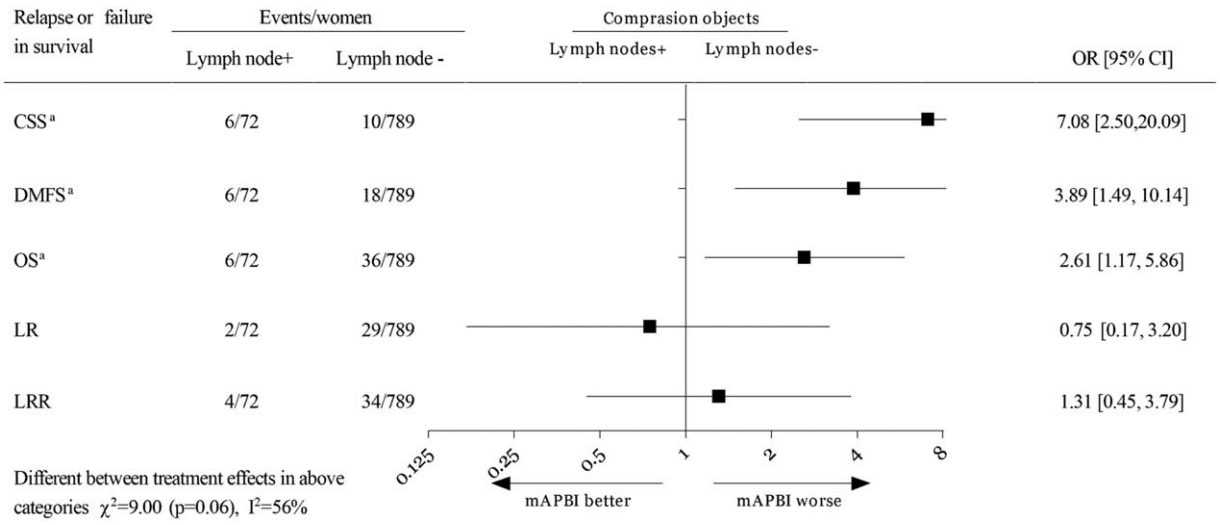

Figure 3. The comparison in lymph node-positive vs node-negative of disease recurrence and failure in survival.

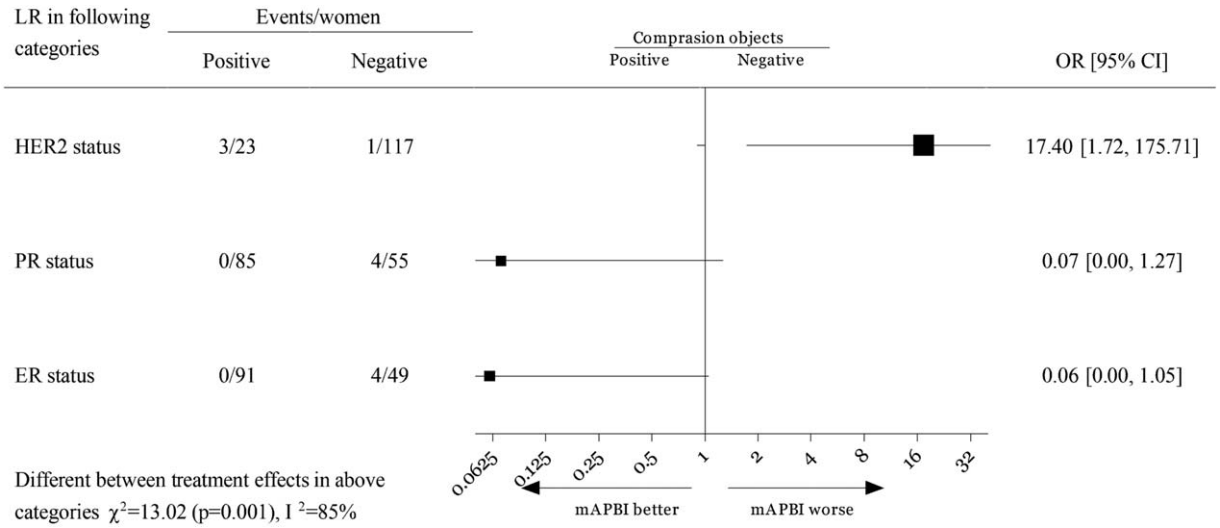

Figure 4. The local recurrence in the following categories: ER-positive vs ER-negative, PR-positive vs PR-negative and HER2-positive vs HER2-negative.

increasing trend in node negativity cohort compared to node positivity cohort (98% vs 90%; $P=.06$). Combined with our results, the failure in survival is further reduced when treated with APBI via multilumen interstitial brachytherapy, especially for 5-year CSS, DMFS, and OS in node-negative women.

Several oncologists have researched the prognostic factors affecting the incidence of LR in breast patients with APBI treatment.[30,31] In the study of Cannon et al,[32] a poor prognostic factor is ER negative status, independently related to increased risk of LRR, which is matched with our outcomes. A small number of studies have also evaluated the effect of HER2 status on the LR rate. Hattangadi-Gluth et al[33] report the identical results as our conclusion, whose study shows that the LR rate of HER2-positive tumor is significantly higher than negative one.

Furthermore, we systematically assessed the RT-related toxicity in women underwent mAPBI. In the acute toxicity, the first common complication is dermatitis, and the lowest one is the implant infection. In the late toxicity, fibrosis takes the highest incidence, and least frequent complication is seroma.

The GEC-ESTRO trial recruited 1182 low-risk patients to compare the results of RT-associated toxicity between WBI approach (n=552) with mAPBI approach (n=663), which illustrated that the mAPBI group had a significantly lower incidence of dermatitis than WBI group (Grade1–3, 19.2% vs 92%; $P<.0001$), but with a significantly increased morbidity of hematoma (Grade1–2, 20% vs 2.2%; $P<.0001$) and implant infection (Grade 1–3, 4.7% vs 2.2%; $P=.005$). There was no statistical difference between the 2 ways induced breast pain ($P=.23$).[34] Different from our results, this study concludes that breast pain is the first common complication induced by mAPBI and reports an incremental morbidity of hematoma and dermatitis. However, the implant infection has the lowest incidence of all acute toxicities, which is concordant to our results. Some reports conclude that the rate of implant infection is between 0% and 11%.[35–40] All patients who accept skin antiseptics and oral antibiotic prophylaxis daily for at least 8 days

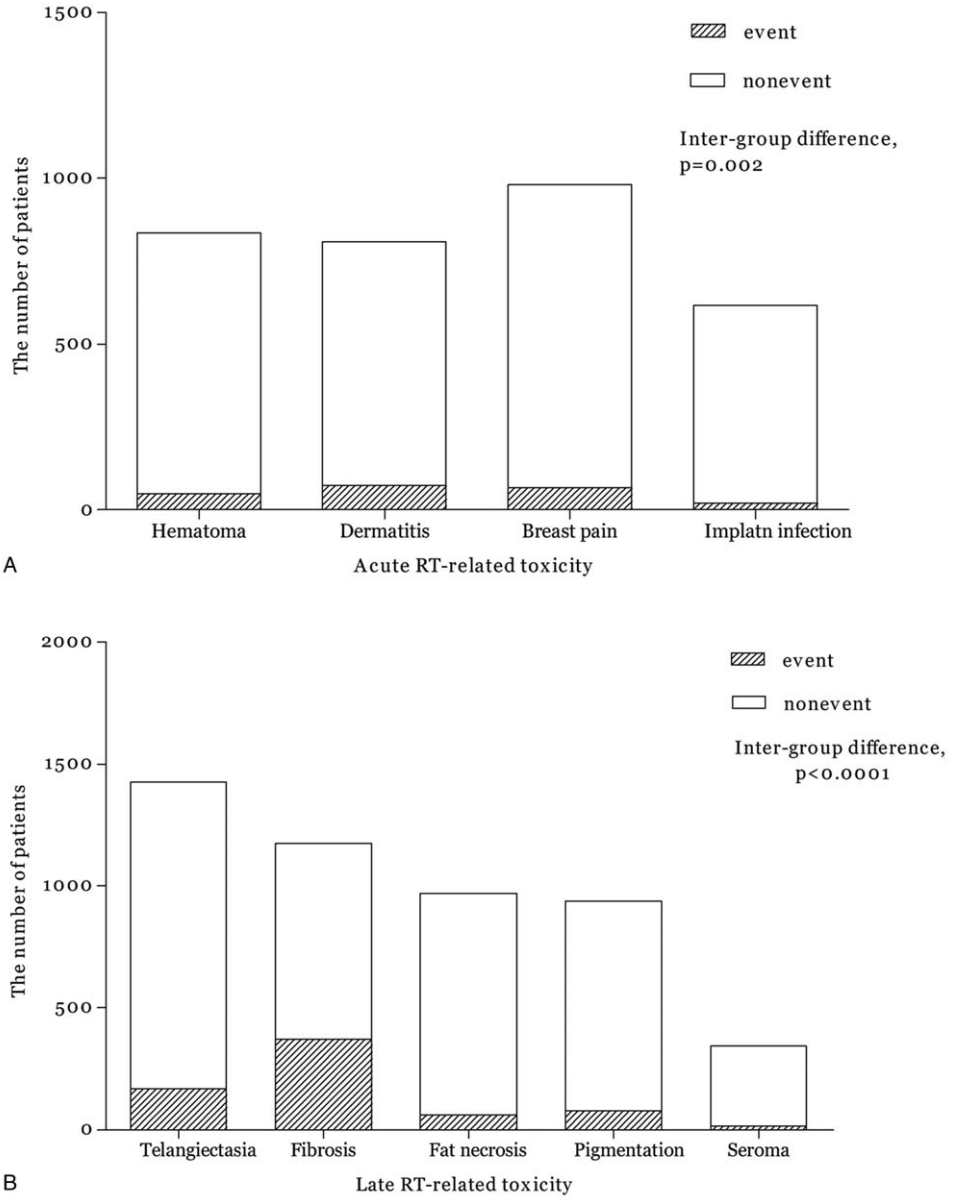

Figure 5. The acute and late RT-related toxicities.

can effectively avoid its occurrence that mainly limited to the entry and exit points of the after-loading tube.[41]

Regarding the late RT-related toxicity followed by treatment with mAPBI, the published literatures mainly focus on describing the incidence of telangiectasias, fibrosis and fat necrosis. Some working groups report that the incidence of telangiectasias ranges from 3.7% to 22.7%,[35,42] with an increased trend as time changing, the rate of fibrosis that occurs most frequently is between 29.5%-42.2%,[35,42] as well as morbidity of fat necrosis ranges from 2.3% to 24.2%[35,40], which are all matched with us. It is worth noting that fibrosis is a combined sequela from postoperative changes and irradiation effects.[35,43,44] Thus, it is difficult to estimate whether the high incidence of this complication is entirely caused by radiotherapy. In the future, we can compare the occurrence of fibrosis between APBI therapy alone with APBI therapy plus surgery to judge the extent of operational effects on its formation according to the difference between the 2 arms.

5. Conclusion

For the early stage breast cancer patients treated with mAPBI therapy, HER2-overexpression subtype compared with other subtypes has a significantly increased disease recurrence and failure in survival, of which in lymph node-positive status is also significantly higher than the negative one. In addition, HER2-positive status is associated with increased rate of LR. The most common acute RT-related toxicity is dermatitis and the first rife late RT-associated toxicity is fibrosis.

Author contributions

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Methodology: Biyuan Zhang.
Project administration: Lijiu Zhang.
Resources: Lin He, Lijiu Zhang.

Software: Lin He.
Supervision: Lijiu Zhang, Yuhua Song.
Validation: Lijiu Zhang, Yuhua Song.
Visualization: Yuhua Song.
Writing – original draft: Yang Lv, Lin He, Chao Wang.
Writing – review & editing: Lin He.
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