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CANCER INNOVATION

REVIEW

Accelerated partial breast irradiation: Current evidence and future developments

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Abstract

Whole breast irradiation after breast-conserving surgery for early breast cancer has become one of the standard treatment modes for breast cancer and yields the same effect as radical surgery. Accelerated partial breast irradiation (APBI) as a substitute for whole breast irradiation for patients with early breast cancer is a hot spot in clinical research. APBI is characterised by simple high-dose local irradiation of the tumour bed in a short time, thus improving convenience for patients and saving costs. The implementation methods of APBI mainly include brachytherapy, external beam radiation therapy, and intraoperative radiotherapy. This review provides an overview of the clinical effects and adverse reactions of the main technologies of APBI and discusses the prospects for the future development of APBI.

KEYWORDS

accelerated partial breast irradiation, brachytherapy, breast cancer, breast conserving surgery, external beam radiation therapy, intraoperative radiotherapy

1 | BACKGROUND

Breast cancer is the most common cancer in women. In the 1970s, the local treatment of breast cancer changed from radical surgery, including simple mastectomy or modified radical mastectomy, to breast-conserving surgery (BCS). BCS combined with assisted whole breast irradiation (WBI), collectively known as breast-conserving therapy (BCT), is one of the standard treatments for breast cancer. Multiple prospective randomised trials with long-term follow-up have shown that there is no significant difference between BCT and modified radical mastectomy regarding overall survival (OS) and disease-free survival (DFS) [1–3].

Standard WBI typically includes daily radiation therapy for the entire breast with a dose of 45–50 Gy for 6–7 weeks. For many patients, WBI typically involves

Abbreviations: 3D-CRT, three-dimensional conformal radiotherapy; APBI, accelerated partial breast irradiation; BCS, breast-conserving surgery; BCT, breast-conserving therapy; CI, confidence interval; DFS, disease-free survival; EBRT, external beam radiation therapy; HR, hazard ratio; HRQoL, health-related quality of life; IBTR, ipsilateral breast tumour recurrence; IMRT, intensity modulated radiotherapy; IORT, intraoperative radiotherapy; IQR, interquartile range; MIBT, multicatheter interstitial brachytherapy; OS, overall survival; PBI, partial breast irradiation; RT, radiotherapy; WBI, whole breast irradiation.

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a 10–16 Gy boost to the tumour bed to further reduce local recurrence. In 2018, the American Society of Radiological Oncology (ASTRO) issued the latest WBI evidence-based guidelines. For patients with invasive breast cancer, hypofractionated WBI is preferred, that is, approximately 40–42.5 Gy/15–16 f. For patients without a high risk of recurrence, the tumour bed supplement should be 10 Gy/4–5 f. For patients with a single high risk of recurrence with a positive margin or those with insufficient incisal margin combined with young age and other composite high risks of recurrence, a boost of higher dose fraction, 14–16 Gy/7–8 f or 12.5 Gy/5 f, can be used [4]. Multiple international randomised studies have shown that hypofractionated WBI can achieve the same local control rate, tumour-free survival rate, and OS rate as conventional fraction modes [5–9], while yielding lower acute toxicity reactions and good cosmetic results [10–12]. With women's concern for breast health and the popularity of breast cancer screening, an increasing number of breast cancers are detected at an early stage, giving many women the opportunity to undergo BCS.

BCT studies have shown that most local breast cancer recurrence occurs at the site of the primary tumour [13, 14]. Pathological studies indicated that in over 90% of cases, residual microlesions are usually located within 1.5 cm of the primary tumour [15]. Combining advanced computed tomography (CT) plans and modern radiation therapy techniques, researchers hypothesise that only targeting the primary tumour for radiotherapy with 1–2 cm expansion will achieve local control similar to WBI. Therefore, the concept of APBI has been proposed, which involves using a higher single-segmented dose (greater than 2 Gy) to provide therapeutic radiation only to the tumour bed rather than the entire breast. Compared with the 3–5-week treatment duration of WBI, this strategy allows for treatment to be provided in a shorter time frame (1 week or less), thereby saving costs and improving resource utilisation at the treatment centre. The shorter treatment duration is also more convenient for patients. APBI may have fewer potential acute adverse reactions [16], and studies have shown that as the total treatment time decreases, tumour control may be improved. Early adopters also concluded that when only a portion of the breast was irradiated, the cosmetic results for the breast were improved, and the lungs and heart were protected.

APBI is mainly administered by brachytherapy, external beam radiation therapy (EBRT), and intraoperative radiotherapy. Modern studies of APBI begin with brachytherapy and have shown good local control and cosmetic effects on the breast [17–19]. Other options have been subsequently examined, including intraoperative radiation therapy, where a radiation source or applicator is positioned inside the surgical cavity during surgery to treat the tumour bed [20, 21]. Brachytherapy and intraoperative radiotherapy are not readily available to most patients since they need specialised equipment, physician training, and resources. Recently, APBI technology has focused on external radiotherapy [22–27]. External radiotherapy is a noninvasive treatment technique that mainly includes three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) techniques, making it the most accessible and cost-effective method.

2 | APBI TECHNOLOGY

2.1 | Brachytherapy

In 2023, GEC-ESTRO published the 10-year follow-up results of a multicentre, phase III, noninferiority randomised trial of APBI versus WBI using multicatheter brachytherapy [17]. The study included 1184 patients with early-stage, low-risk invasive and ductal carcinoma in situ who underwent BCS between April 2004 and July 2009. The patients were randomly assigned to the APBI and WBI groups: 633 patients received APBI using multicatheter brachytherapy, high-dose-rate brachytherapy of 30.1 Gy/7 f or 32.0 Gy/8 f within 5 days, or pulsed dose-rate brachytherapy of 50 Gy within 5 treatment days; and 551 patients received WBI with 50 Gy of radiation once a day for a total of 25 fractions within 5 weeks, with a supplemental boost of 10 Gy to the tumour bed. The primary endpoint was ipsilateral local recurrence, with a noninferiority margin (defined as the 5-year outcome) of 3 percentage points for the difference in recurrence rates. The median follow-up was 10.36 years (interquartile range [IQR] 9.12–11.28), with a 10-year ipsilateral local recurrence rate of 1.58% (95% confidence interval [CI]: 0.37–2.8) in the WBI group and 3.51% (1.99–5.03) in the APBI group. The difference in the 10-year local recurrence rate between the two groups was 1.93% (95% CI: −0.018 to 3.87; $p = 0.074$). Further subgroup analysis, classified by age, menopausal status, hormone receptor status, node status, histological type, tumour size and grade, and use of systemic therapy, found that only Grade 2–3 tumours and use of systemic therapy, especially anti-hormone therapy, affected the difference in local recurrence rates between the two groups. During a follow-up of 7.5 or 10 years, or both, adverse events, mainly Grades 1 and 2, occurred in 234 (60%) of 393 patients in the WBI group and 314 (67%) of 470 patients in the APBI group. The incidence of Grade 3 late adverse reactions associated with treatment was significantly lower in the APBI group than in the WBI

group (7 of 470 patients [1%] vs. 17 of 393 patients [4%]; $p = 0.021$). At 10 years, fibrosis was the most prevalent Grade 3 adverse event (6 of 313 WBI patients [2%] and 3 of 375 APBI patients [1%], $p = 0.56$), and there were no Grade 4 adverse reactions or deaths associated with treatment [17]. The long-term follow-up results from this randomised phase III trial with sufficient statistical power show that postoperative APBI using multi-catheter brachytherapy after BCS is as effective and safe as postoperative WBI for selected patients with early-stage breast cancer. Therefore, for patients with low-risk early-stage breast cancer who choose BCS and post-operative radiation therapy, APBI using multi-catheter brachytherapy should be considered as an attractive treatment option.

The Mammo Site® (Hologic Inc.) intracavitary breast brachytherapy device was developed as an alternative to single-channel balloon-based multicatheter interstitial brachytherapy (MIBT) and received FDA approval in 2002 to simplify the administration of APBI and make it more independent on center expertise in MIBT. A deflated balloon applicator is placed in the BCS cavity during surgery or as a second postoperative procedure. A large registration study was carried out on 1449 patients with a treatment regimen of 34 Gy divided into 10 sessions. At a follow-up of 63 months, the 5-year local failure rate was 3.8%. At 84 months, the aesthetic satisfaction rate was 90.6%. However, the incidence of fat necrosis and infection was higher, at 2.5% and 9.6%, respectively [19]. Wallace et al. [28] reported the findings of a prospective phase I/II trial that involved 45 patients receiving 28 Gy balloon brachytherapy with four exposures of 7 Gy each. At a median follow-up of 11.4 months, relatively high toxicity was observed in four cases (two symptomatic) of fat necrosis and 4% [2] of rib fractures, reflecting the lower dose distribution of balloon-based bandage brachytherapy (BAB) in accordance with the surrounding organs at risk (OARs) compared with MIBT [28].

2.2 | EBRT

The RAPID multicentre, randomised, and noninferiority trial compared the effectiveness and toxicity of APBI using 3D-CRT and WBI. A total of 2135 women ≥40 years old who had undergone BCS for ductal carcinoma in situ or breast cancer with negative lymph nodes and tumour ≤ 3 cm were randomised to the APBI and WBI groups. In the APBI group, 3D-CRT (90%) or IMRT (10%) was used at 38.5 Gy/10 f twice daily in the segmentation mode. The WBI group was treated with segmentation mode of 50 Gy/25 f or 42.5 Gy/16 f. The median follow-up was 8.6 years. In the APBI group, the 8-year cumulative recurrence rate in the ipsilateral breast was 3.0% (95% CI: 1.9–4.0); in the WBI group, it was 2.8% (1.8–3.9). The HR of APBI versus WBI was 1.27 (90% CI: 0.84–1.91). The preset noninferiority criteria were met. There were no statistical differences in the treatment effects across different subgroups, stratified by age, histology, tumour size, ER status, tumour grade, adjuvant therapy, and APBI suitability. The two groups were equivalent regarding DFS, OS, and breast cancer mortality. In the APBI group, the incidence of acute radiation toxicity ≥ Grade 2 was 28%, which was lower than that in the WBI group (45%, $p < 0.0001$), but the incidence of late radiation toxicity ≥ Grade 2 was higher (32% vs. 13%, $p < 0.0001$). The proportion of adverse cosmetic effects was also higher in the APBI group than the WBI group, with an absolute difference of 17.7% at 7 years and a 95% CI of 12.9–22.3 [22]. The RAPID results indicate that APBI using 3D-CRT technology is not inferior to WBI in avoiding ipsilateral breast recurrence. While less acute toxicity was observed, an increase in late toxicity and adverse cosmetic effects, which may be associated with twice-daily treatment, requires caution in the use of this regimen.

IMRT is recommended as the preferred technique for APBI in the 4th Edition of the NCCN Breast Cancer Clinical Practice Guidelines in 2023 for better dose uniformity and better protection of normal tissue than 3D-CRT.

A randomised phase III study from Florence compared APBI using IMRT with WBI over 10 years of follow-up. A total of 520 patients were randomly assigned to the APBI and WBI groups ($n = 260$/group) between 2005 and 2013, with over 90% having characteristics associated with a low risk of recurrence. The APBI group received a radiation dose of 30 Gy/5 f once every other day. The WBI group received 50 Gy/25 f, plus a tumour bed boost of 10 Gy/5 f, once a day. The median follow-up was 10.7 years. The 10-year cumulative recurrence rate in the ipsilateral breast was 2.5% ($n = 6$) in the WBI group and 3.7% ($n = 0.9$) in the APBI group (HR = 1.56; 95% CI: 0.55–4.37; $p = 0.40$). The 10-year OS of both groups was 91.9% (HR = 0.95; 95% CI: 0.50–1.79; $p = 0.86$). The specific survival rate of patients with breast cancer was 96.7% in the WBI group and 97.8% in the APBI group (HR = 0.65; 95% CI: 0.21–1.99; $p = 0.45$). No factors such as age, hormone receptor status, nodal status, tumour size and grade, or risk group influenced the treatment effects for WBI and APBI. Acute toxicity ($p = 0.0001$) and late toxicity ($p = 0.0001$) of the APBI group were significantly reduced, and cosmetic outcomes were significantly improved as assessed by both patients ($p = 0.0001$) and physicians ($p = 0.0001$) [26]. The study reported a low 10-year cumulative incidence of IBTR in

early-stage breast cancer patients who received external beam APBI using IMRT technology five times daily; there was no difference from that after WBI treatment. Treatment-related acute and late toxicity and cosmetic effects were clearly favourable for APBI.

UK IMPORT LOW reported the 5-year results from a noninferiority study of nonaccelerated partial breast irradiation (PBI) using IMRT [27]. From 2007 to 2010, 2018 female patients with tumours sized 3 cm or smaller (pT1–2) and 0–3 positive axillary lymph nodes (pN0–1) undergoing BCS were randomised into three groups in a 1:1:1 ratio: the PBI group (40 Gy/15 f), the WBI dose reduction group (36 Gy/15 f for the whole breast and 40 Gy/15 f for the tumour bed), and the WBI control group (40 Gy/15 f for the whole breast). The median follow-up was 72.2 months, and 18 patients developed local recurrence (including 6 patients in the PBI group, three in the WBI dose reduction group, and nine in the WBI control group). The 5-year cumulative local recurrence rates were 0.5% (95% CI: 0.2–1.4), 0.2% (95% CI: 0.02–1.2), and 1.1% (95% CI: 0.5–2.3), respectively. The 5-year absolute difference in estimates of local recurrence was −0.73% (−0.99–0.22) in the WBI dose-reduction group and −0.38% (−0.84 to 0.90) in the PBI group compared with the WBI control group. Both the WBI dose reduction group and the PBI group showed noninferiority compared with the WBI control group, with a critical risk greater than 2.03 ($p = 0.003$ and $p = 0.016$, respectively). Local recurrence, distant recurrence, and OS were similar among the three groups. Photographs, patients, and clinical evaluations recorded similar adverse events in the WBI dose reduction group and the PBI group, with significant reductions in adverse reactions in both groups compared with the WBI control group, including changes in breast appearance ($p = 0.007$ for the PBI group) and breast hardening ($p = 0.002$, WBI dose reduction group; $p < 0.0001$, PBI group) [27].

The results of the above three clinical trials showed that regardless of which external radiotherapy technique was used, the recurrence rate in the ipsilateral breast after APBI was comparable to that after WBI. Therefore, the application of EBRT in APBI was supported.

NSABP B-39/RTOG 0413 is a multicentre, Phase III randomised controlled study using an equivalent design, with APBI using 3D-CRT (73%) (38.5 Gy/10 f twice a day) or brachytherapy (34 Gy/10 f twice a day) and brachytherapy using single cavity (21%) or multicatheter (6%) techniques compared with WBI (50 Gy/25 f, ±10–16 Gy tumour bed boost). From 2005 to 2013, a total of 4216 women ≥ 18 years old with tumours ≤ 3 cm and 0–3 positive axillary lymph nodes were enroled. At a median follow-up of 10.2 years, the 10-year cumulative recurrence rate in the ipsilateral breast (primary endpoint) after APBI was 4.6% (95% CI: 3.7–5.7) and that after WBI was 3.9% (3.1–5.0); the HR was 1.22 (90% CI: 0.94–1.58), which did not meet the preset equivalence criteria. Compared with WBI, APBI resulted in a shorter relapse-free interval (91.8% vs. 93.4%), with an HR of 1.33 (95% CI: 1.04–1.69, $p = 0.02$). Breast cancer mortality and OS were similar between groups. There were no variations in the treatment effects between the subgroups classified by menopausal status, intent to receive chemotherapy, disease stage, hormone receptor status, and invasive cancer risk. APBI was also advantageous in patients with invasive tumours sized 10 mm or smaller. Acute and late toxicities were not reported separately. The overall toxicity characteristics were similar, with Grade ≥ 3 toxicity slightly more common in the APBI group (10% vs. 7%) [23]. The cosmetic outcomes of the group of patients who received or did not receive chemotherapy were evaluated by the patients, the attending physician, and a photographic review. The results varied. The patient and photographic evaluations showed equivalence between the two groups. According to the doctor's evaluation, the cosmetic outcome of APBI patients at 36 months was worse than that of WBI patients [29]. However, in controlling IBTR, APBI did not meet the criteria equivalent to WBI in BCT. It may be that the trial had a broad range of inclusion criteria, resulting in a large number of heterogeneous patients and having sufficient ability to test treatment equivalence, but it was not designed to detect the equivalence of patient subgroups or the outcomes of different APBI technologies. However, for early breast cancer patients, the absolute difference in the 10-year cumulative recurrence rate in the ipsilateral breast between the APBI and WBI groups was less than 1%, suggesting APBI may be an acceptable alternative for some female patients.

2.3 | Intraoperative radiotherapy

Intraoperative radiotherapy refers to the application of local radiation therapy during the surgical process, including electron therapy, brachytherapy, and photon therapy. Two phase III clinical trials (ELIOT [21] and TARGIT-A [20]) are large clinical studies on the application of APBI in BCS for early breast cancer.

In the ELIOT trial, 1305 female patients with breast tumours ≤ 2.5 cm in diameter who underwent BCS between 2000 and 2007 were randomised into two groups: the ELIOT group (a single dose of 21 Gy intraoperative radiotherapy with electrons to the tumour bed) ($n = 651$) and the WBI group (routine segmentation of 50 Gy/25 f, plus a 10 Gy tumour bed boost) ($n = 654$). The median follow-up was 12.4 years, with 86 patients

(7%) developing IBTR, including 70 in the ELIOT group (11%) and 16 in the WBI group (2%), with an HR of 4.62 (95% CI: 2.68–7.95, $p < 0.0001$). The 5-year, 10-year, and 15-year IBTR incidence rates of the two groups were 4.2% versus 0.5%, 8.1% versus 1.1%, and 12.6% versus 2.4%, respectively. In stratified analysis, the risk of IBTR in the ELIOT group was higher than that in the WBI group in all subgroups, including age, histology, pathological tumour size, positive nodes, resection margins, tumour grade, oestrogen receptor status, progesterone receptor status, proliferative index (Ki-67), HER2 status, and molecular subtype groups. However, there was no difference in mortality between the two groups (98 deaths in the ELIOT group and 95 deaths in the WBI group), with an HR of 1.03 (95% CI: 0.77–1.36, $p = 0.85$) [21]. The trial did not collect long-term data on adverse reactions.

TARGIT-A was a randomised, controlled, noninferiority clinical study including women who were eligible for breast preservation, ≥45 years of age, and with tumours ≤3.5 cm, N0–1, M0, and single focal invasive ductal carcinoma. Between 2000 and 2012, the trial involved 2298 women; 1140 patients were randomly assigned to the TARGIT-IORT group (intraoperative tumour bed surface receiving 50 kV X-ray beams at 20 Gy), and 1158 patients were assigned to the WBI group. A risk adaptation approach was used, and approximately 20% of patients with high-risk features found in the final pathological examination after intraoperative APBI were given an additional WBI equivalent to 50 Gy. At a complete 5-year follow-up, the risk of local recurrence was 2.11% in the TARGIT-IORT group and 0.95% in the WBI group (the difference was 1.16%, 90% CI: 0.32–1.99). The preset equivalent standards were met. The median follow-up was 8.6 years. Local recurrence-free survival, OS, mastectomy-free survival, distant metastasis-free survival, and breast cancer mortality were similar between groups. However, in the TARGIT-IORT group, the mortality rate from other causes was significantly reduced (HR = 0.59; 95% CI: 0.40–0.86, $p = 0.005$) [20]. Further subgroup analysis indicated no difference in local relapse-free survival between the TARGIT-IORT group and the WBI group in each tumour subgroup. Unlike after WBI, the prognosis of local recurrence after TARGIT-IORT is good [30]. The TARGIT-A study findings support the intraoperative use of APBI instead of WBI in early-stage breast cancer patients who meet the study enrolment criteria and are risk-adapted.

From the results of the above two large clinical trials of intraoperative radiotherapy, it is necessary to carefully select appropriate patients for intraoperative radiotherapy, and strict screening conditions for intraoperative radiotherapy patients may be a hot spot for further research.

2.4 | Other APBI technologies

Stereotactic body radiation therapy (SBRT) can accurately determine the size and position of the target area by connecting with imaging devices such as MR or CT. Lozza et al. [31] applied CyberKnife to APBI and published preliminary results in 2018, indicating that CK-APBI is feasible and safe for the treatment of early-stage breast cancer, with moderate acute and late toxicity and good cosmetic effects. CK-APBI has the technical features of real-time tracking, respiratory motion management, and millimetre-level accuracy, maximising target coverage while protecting normal tissues from unnecessary high doses of radiation. The treatment time was approximately 60 min (35–120 min), the irradiation dose was 30 Gy/5 f, and the median number of irradiation fields was 180 (IQR: 107–213). Although CK-APBI is highly innovative, breast tissue is more difficult to locate than brain or chest tissue because of its mobility and flexibility. The number of patients enroled thus far is small, and long-term follow-up data will be worth exploring.

Proton radiotherapy uses proton beams instead of classical photon or X-ray beams. Because of the presence of the Bragg peak, high-dose radiation will sharply decrease after reaching the endpoint, reducing the radiation impact on distal normal tissues. Therefore, important distal organs such as the lung and heart can be protected during breast irradiation [32]. A Phase II trial using proton APBI used a split dose of 34 Gy/10 f twice a day. The midterm results showed a local control rate and survival rate of 100% at 1 and 2 years [33]. However, proton radiotherapy is currently expensive, and its promotion and application require further exploration.

3 | SELECTION OF A SUITABLE POPULATION

At present, most studies choose early-stage breast cancer patients with a low risk of recurrence. In 2009, ASTRO issued a consensus for the first time [34], dividing patients into three groups: patients in the “suitable” group can receive APBI without participating in clinical trials; patients in the “need to be cautious” group should be cautious when receiving APBI without participating in clinical trials; and patients in the “unsuitable” group who receive APBI without participating in clinical trials are generally not considered to have a guarantee of efficacy. The 2016 ASTRO Consensus defined patients who are BRCA-negative, age ≥50 years, and meet one of the following criteria as “suitable” for APBI: invasive

ductal carcinoma, primary tumour ≤2 cm (pT1), negative margin width ≥2 mm, no vascular invasion, and ER-positive; or low/moderate nuclear grade, DCIS detected by screening, with primary tumour ≤2.5 cm and negative margin width ≥3 mm [35]. In 2018, a new interpretation of the guidelines was published [36], which answered the question of population selection for APBI and which patients can receive IORT.

With the publication of the findings from the two randomised clinical trials of IORT with ELIOT (21) and TARGIT-A (20), new recommendations were made in the guidelines: (1) patients who strictly meet the requirements of the "suitable" group can receive intra-operative electron therapy; and (2) intra-operative photon therapy can only be applied in clinical trials [36].

4 | FUTURE DIRECTIONS

For patients with low-risk breast cancer, APBI is an appropriate treatment to lower the risk of IBTR after BCS. The latest large studies have demonstrated the tolerability and effectiveness of APBI. To date, trials have shown that multicatheter brachytherapy, or EBRT, appears to be the most effective. The exploration of reducing the number of fractions in the postoperative PBI setting may have reached a plateau. The typical regimen is a five-fraction schedule, which may be a suitable compromise in terms of effectiveness, safety, and health-related quality of life (HRQoL) [37]. The negative results of most intraoperative single-fraction PBI trials have been considered [20, 21, 38–40]. The potential benefits of preoperative PBI open a new frontier [41], despite concerns about the optimal dose, fractionation, and technique [42–47]. Postoperative PBI thus remains the gold standard of care.

Adjuvant endocrine therapy alone, without breast irradiation, is another significant treatment-downgrading strategy being researched for low-risk breast cancer. This approach has been encouraged for patients with hormone receptor positivity, pT1N0, and an age of 70 years or older who are scheduled for adjuvant endocrine therapy [48, 49]. Several cohort studies and randomised trials are currently evaluating patients ≥50 years old (NCT01791829, NCT 02653755, NCT02400190, NCT02889874, and NCT0413 4598) [50, 51].

Meattini et al. [52] proposed a potential personalised RT algorithm for early-stage, low-risk breast cancer on the basis of genome data. Currently, international recommendations in favour of PBI over WBI are based on clinicopathological risk factors [35, 53]. Because genome-based predictive relapse scores provide the risk of local recurrence and distant metastasis, combining them with clinicopathological risk factors can further improve the optimal local treatment strategy. Regarding treatment optimisation, the degradation or enhancement of RT can be tested on the basis of genomic scores, regardless of clinicopathological characteristics. Clinical trials are urgently required to explore these hypotheses. Without impacting oncologic outcomes, more individualised RT and selective endocrine therapy may improve cost-effectiveness and patient HRQoL.

AUTHOR CONTRIBUTIONS

Dandan Song: Writing—original draft (equal); writing—review & editing (equal). **Honghong Zhang**: Writing—original draft (equal); writing—review & editing (equal). **Chengbo Ren**: Conceptualization (supporting); writing—review & editing (supporting). **Ning Zhan**: Writing—review & editing (supporting). **Liangxi Xie**: Conceptualization (lead); writing—review & editing (equal). **Wenjia Xie**: Conceptualization (lead); writing—review & editing (equal).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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Not applicable.

INFORMED CONSENT

Not applicable.

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