Review Article

2021 updates in postoperative radiotherapy section of Chinese Society of Clinical Oncology Breast Cancer guideline

Lu Cao[1#], Jun Zhang[2#], Jiayi Chen[1], Zefei Jiang[3]

[1]Department of Radiation Oncology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; [2]Department of Radiation Oncology, The Fourth Hospital of Hebei Medical University/Hebei Cancer Hospital, Shijiazhuang, China; [3]Cancer Center of Chinese PLA General Hospital, Beijing, China

Contributions: (I) Conception and design: J Chen; (II) Administrative support: Z Jiang; (III) Provision of study materials or patients: L Cao, J Zhang; (IV) Collection and assembly of data: L Cao, J Zhang; (V) Data analysis and interpretation: L Cao, J Zhang, J Chen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Jiayi Chen. Department of Radiation Oncology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, 197 Ruijin Second Road, Shanghai 200025, China. Email: chenjiayi0188@aliyun.com.

Abstract: As an integral part of the Chinese Society of Clinical Oncology Breast Cancer (CSCO BC) guideline, the radiation therapy (RT) section was issued in 2017 and updated annually. The panel members make risk-adapted stratified practical clinical recommendations of postoperative RT which reflect the latest global literature in the field and high-quality clinical trials from Chinese academic centers in a timely manner. Considering another function of encouraging physicians to participate in clinical trials, the footnotes of the postoperative RT section highlight the controversies that existed in decision making, the importance of modern RT techniques in decreasing toxicity, and the main evidence supporting treatment recommendations in each clinical scenario, including "grey zones". The postoperative RT section of the 2021 CSCO BC guideline can be summarized as follows: (I) prioritize the routine clinical practice of hypofractionated regime in postoperative RT, especially in breast-conserving patients receiving whole-breast irradiation without regional nodal irradiation (RNI). Apart from 3-week based moderated hypofractionated whole breast irradiation (WBI), the one week schedule is also included in the recommendation for selective node negative patients. (II) Refine risk-adapted decision-making of RT, including nodal irradiation in T1-2 N1 patients and omitting irradiation in low risk patients receiving breast conservative surgery; (III) recommend comprehensive criteria of postoperative RT technical details. The panel members hope that evidence-based recommendations continuously contribute to an improved standardization of BC postoperative radiotherapy and to synchronizing the clinical practice following the results of the latest high-quality clinical research.

Keywords: CSCO BC guideline; postoperative radiotherapy; hypofractionated regimen; risk-adapted decision-making; technical details

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Introduction

As an important part of breast cancer multidisciplinary treatments, radiation therapy (RT) has been an integral part of the Chinese Society of Clinical Oncology Breast Cancer (CSCO BC) guideline since the first version was issued in 2017 and with each annual update. Different from the raditional writing style, the CSCO BC guideline adopts a step-by-step recommendation along with the mindset of diagnosis and treatment in routine clinical practice and focuses heavily on availability and applicability. The postoperative RT section follows these unique features and

makes risk-adapted stratified recommendations according to the type of primary surgery, and clinical and pathological stage of the disease, incorporated with different systemic treatments. The panel of the CSCO BC guideline takes care to reflect the latest global literature in the field and also to update the recommendation based on high-quality clinical trials from Chinese academic centers in a timely manner.

In addition to practical clinical recommendations, another function of the guideline is to encourage physicians to participate in clinical trials. Considering these functions, the footnotes of the postoperative RT section clearly present the controversies existing in decision making, and elaborate the main evidence supporting treatment recommendations in each clinical scenario, including "grey zones". The potential advancement of modern RT techniques in decreasing toxicity are also discussed.

The following contents of the paper will detail the updates in the postoperative RT section of the 2021 CSCO BC guideline based on the aforementioned principles.

Increased priority in recommendation of hypofractionation regimen in postoperative RT

The 3-week regimen of moderated hypofractionated (HF) whole breast irradiation (WBI) in invasive breast cancer

Long-term follow-up of 4 randomized clinical trials has shown the equivalent efficacy and toxicity between HF regimen of 40–42.5 Gy in 15–16 fractions and conventional fractionated (CF) regimen (CF) of 50 Gy in 25 fractions in patients treated with WBI (1-3). Considering the advantages of HF regimen in the convenience of treatment, economizing iatrical resource, and minimizing non-medical costs to patients, the first edition of the CSCO BC guideline made the Grade 1B recommendation on the utility of HF regimen of 40–42.5 Gy in 15–16 fractions in patients receiving RT to the breast only. Following this recommendation, the acceptance and adoption of HF have been increasing in recent years in China. Subsequent to the strong evidence HF in WBI in a large, prospectively collected cohort from British Columbia, Lalani *et al.* (4) verified the efficacy of HF-WBI across breast cancer molecular subtypes. The study cohort included 5,868 patients with stage I–III breast cancer between 2005–2009 who received breast-conserving surgery (BCS) or mastectomy followed by WBI or chest wall irradiation. The median age was 58 years old. A total of 94.5% of the whole cohort (n=5,544) were pT1–2 and 57.2% of participants (n=3,354) were pN0. In the study, 76% of participants (n=4,429) were treated with HF. At a median follow-up of 10.8 years, the 10-year local recurrence-free survival (LRFS) of the entire cohort was 97.1%. Although triple-negative patients had the least favorable 10-year LRFS of 93.5%, in each of the 4 molecular subtypes, there was no significant difference in 10-year LRFS between participants treated with HF versus CF. The results of this study demonstrate that the application of HF-WBI should not be restricted by molecular subtypes. Base on the evidence of this study and accumulating evidence from clinical trials and real-world data published in recent years (4-8), this year's updated guideline has formally recommended an HF regimen as the preferred option for patients with invasive breast cancer who receive WBI only.

The one-week regimen of ultra HF-WBI

The FAST Trial (CRUKE/04/015) was a randomized clinical trial with the purpose of evaluating normal tissue effects (NTE) and disease outcomes of a 5-fraction regimen of WBI (9). A total of 915 women aged ≥50 years with pT1–2 pN0 breast cancer and without chemotherapy were randomly assigned to receive WBI using HF regimen of 30 or 28.5 Gy in 5 once-weekly fractions or CF regimen of 50 Gy in 25 daily fractions. The median follow-up of 9.9 years showed no significant differences between 28.5 Gy and 50 Gy in rates of mild/marked change in photographic breast appearance at 2 or 5 years [odds ratio (OR) =1.10; P=0.686] and absolute differences in the 10-year rate of any moderate/marked breast NTE (5%, P=0.184). However, the rates of mild/marked change in photographic breast appearance at 2 or 5 years (OR =1.64; P=0.019) and 10-year rate of any moderate/marked breast NTE (absolute difference: 9%, P=0.032) were significantly higher for 30 Gy compared with 50 Gy. The estimated cumulative rates of ipsilateral breast events were very low in all 3 groups (50 Gy, 0.7%; 30 Gy, 1.4%; 28.5 Gy, 1.7%). Supported by the safety and efficacy evidence from the FAST trial, the FAST FORWARD trial was initiated to further explore whether the 1-week schedule is non-inferior to a 3-week regimen of HF-WBI in terms of tumor control and late adverse effects (10). A total of 4,096 patients (pT1–3, pN0–1, M0) were randomly assigned to 40 Gy in 15 daily fractions (n=1,361), 27 Gy in 5 daily fractions (n=1,367), or 26 Gy in 5 daily fractions (n=1,368). With a median follow-up of 71.5 months, no significant difference in the 5-year rate of ipsilateral intramammary recurrence (IBTR) between 26 and 40 Gy (1.4% *vs.* 2.1%, P=0.86),

and between 27 and 40 Gy (1.7% *vs.* 2.1%, P=0.67) was found. At 5 years, the rate of any moderate/marked clinician-assessed NTE in the breast or chest wall was 9.9% for 40 Gy, 15.4% for 27 Gy, and 11.9% for 26 Gy, with a significant difference between 40 and 27 Gy (P=0.0003) but not between 40 and 26 Gy (P=0.17). As the first randomized trial of the 1-week regimen of HF-WBI, FAST FORWARD preliminarily has demonstrated that the ultra-short regime could serve as a new option for WBI. As data on long-term follow-up are still pending, this year's updated guideline has not made a formal recommendation on the utility of 1-week regimen of HF-WBI in routine clinical practice, but has highlighted in the footnotes that 26 Gy in 5 daily fractions could serve as an optimal choice for patients who meet the inclusion criteria of the FAST FORWARD trial, which constitutes the first recommendation on the utility of 1-week regimen of HF-WBI in the breast cancer practice guidelines.

The 3-week regimen of HF-WBI in ductal carcinoma in situ (DCIS)

In previous randomized clinical trials of HF-WBI, participants with DCIS represented only a very small part of the whole cohort, and there is a lack of evidence in the adoption of HF regimen in DCIS. The BIG 3-07/TROG 07.01 trial is an international, multicentre, randomized, controlled, phase 3 trial evaluating tumor bed boost and HF regimen in patients with non-low-risk DCIS receiving BCS plus WBI (11). The inclusion criteria were <50 years of age or ≥50 years of age and the presence of 1 or more of the following: palpable tumor, symptomatic presentation, multifocal disease, microscopic tumor size ≥1.5 cm, intermediate or high nuclear grade, central necrosis, comedo histology, and radial surgical margin less than 1 cm. A total of 1,608 DCIS patients were randomized to receive tumor-bed boost (16 Gy in 8 daily fractions), no boost following CF-WBI (50 Gy in 25 daily fractions), or HF-WBI (42.5 Gy in 16 daily fractions) in 1 of 3 randomization categories. The CF-WBI and HF-WBI were delivered to 831 participants and 777 participants, respectively. The 6.6-year follow-up of this trial was reported in the 2020 San Antonio Breast Cancer Symposium (SABCS) (12). There were no significant differences observed in the 5-year rate of LRFS between the CF-WBI group and HF-WBI group in the randomization group A (94% *vs.* 94%, P=0.84) and in all randomized participants (95% *vs.* 95%, P=0.89). The rates of skin and subcutaneous tissue fibrosis (6% *vs.* 15%, P=0.14) and grade ≥2 breast pain (12% *vs.* 16%, P=0.84) also did not differ significantly between the groups. This trial preliminarily confirmed the safety and efficacy of HF-WBI in patients with non-low-risk DCIS. Based on this evidence, this year's updated guidelines for the first time have made a recommendation on the 16 fractions regimen of HF-WBI in patients with non-low-risk DCIS. Considering the median follow-up of the BIG 3-07/TROG 07.01 trial is only 6.6 years, the guideline also warns that long-term follow-up is still needed to ultimately verify the efficacy and safety of HF-WBI in patients with DCIS.

Hypofractionation regimen of tumor-bed boost

In early randomized clinical trials of HF-WBI, the tumor-bed boost was either not allowed or administered at the discretion of radiation oncologists. If a boost was given, it was delivered sequentially using a CF regime of 10–16 Gy in 5–8 fractions. The actual course of RT would be prolonged from 3 weeks to 4–4.5 weeks in patients treated with tumor-bed boost, which would undermine the advantages of the HF regimen. With the widespread adoption of the HF regimen and increasing demand for further compression of the course of RT, research on HF tumor-bed boost has gradually attracted attention. In 2020, the team at the Cancer Hospital Chinese Academy of Medical Sciences published results of a randomized clinical trial of 3-week HF-WBI plus sequential HF tumor-bed boost (8). A total of 729 patients with pT1–2 pN0–3 breast cancers and BCS were randomly allocated to receive WBI with or without regional nodal irradiation (RNI) plus sequential tumor-bed boost, either using HF regimen of 43.5 Gy in 15 fractions with a boost of 8.7 Gy in 3 fractions (HFRT) or CF regimen of 50 Gy in 25 fractions with a boost of 10 Gy in 5 fractions (CFRT). The median follow-up of 73.5 months showed no significant difference in 5-year cumulative incidence of local recurrent with 1.2% in the HFRT group and 2.0% in the CFRT group (P=0.017 for noninferiority). There were also no significant differences in both acute and late toxicities, except that the acute skin toxicity of grade 2-3 in the HFRT group was significantly lower than that in the CFRT group (3.0% *vs.* 7.5%, P=0.019). This study confirmed the efficacy and safety of the combination of HF-WBI and sequential HF tumor-bed boost. Based on this evidence, this year's updated guideline made a grade 1B recommendation on the application of sequential HF tumor-bed boost in patients

receiving WBI.

The 3-week regimen of RNI

Compared with HF-WBI, evidence supporting the efficacy and safety of the 3-week regimen is still premature for RNI, especially with the use of intensity-modulated radiation therapy (IMRT), delivery of irradiation of internal mammary node (IMN), and in patients treated with implant-based breast reconstruction. The first randomized clinical trial of 3-week HF regimen used in RNI was published by the team at the Cancer Hospital Chinese Academy of Medical Sciences in 2019 (13). A total of 820 patients were enrolled and randomly assigned to the CF group (50 Gy in 25 daily fractions) or HF group (43.5 Gy in 15 daily fractions). After a median follow-up of 58.5 months, there was no significant difference in the 5-year rate of locoregional recurrence (8.3% *vs.* 8.1%), 5-year overall survival (OS) (84% *vs.* 86%), and 5-year disease-free survival (DFS) between the HF group and CF groups. There were also no significant differences between the groups in acute and late toxicities, except that rate of grade 3 acute skin toxicity was higher in the CF group compared with the HF group (8% *vs.* 3%, P<0.0001). Based on this trial and increasing evidence supporting the equivalence between CF regime and 3-week regime of HF in terms of radiobiological effect, this year's updated guideline for the first time has made a recommendation on the routine clinical practice of 3-week HF regimen in RNI with the preconditions that IMRT is the preferred technique and strict quality assurance (QA) requirements should be applied. The updated guideline encourages radiation oncologists to conduct or participate in clinical trials to further verify the safety and efficacy of HF-RNI with the use of modern radiotherapeutic techniques, including more comprehensive nodal area and in patients treated with implant-based breast reconstruction.

Updates in accelerated partial breast irradiation (APBI)

With the advantages of shortening the course of RT and reducing radiation exposure of normal tissues, APBI remains as an attractive option for low-risk patients with BCS. Routine clinical practice of APBI was recommended in the first version of CSCO BC for highly selected low-risk patients. Concerns of APBI include the increased risk of late-toxicity, inferior local control compared with using the external beam technique, and limited accessibility of interstitial brachytherapy. Recently, the first phase 3 randomized trial of APBI using the IMRT technique (APBI-IMRT-Florence) provided an alternative strategy for ABPI, which was conducted by the team from the University of Florida (14). A total of 520 patients aged >40 years, tumor size <2.5 cm, and margin ≥5 mm were enrolled after BCS and randomly assigned to APBI group (30 Gy in 5 nonconsecutive once-daily fractions) and WBI group (a total dose of 50 Gy in 25 fractions, followed by tumor-bed of 10 Gy in 5 fractions). There was no significant difference in the 10-year rate of IBTR (3.9% *vs.* 2.6%, P=0.39) and 10-year rate of OS (92.7% *vs.* 93.3%, P=0.97) between the APBI group and WBI group. In terms of safety, the APBI group showed significantly less acute toxicity (P=0.0001) and late toxicity (P=0.0001) and improved cosmetic outcomes as evaluated by both physician (P=0.0001) and patient (P=0.0001), compared with the WBI group. Based on the evidence of better safety and equivalent efficacy associated with APBI shown in the APBI-IMRT-Florence trial, this year's updated guideline recommends that IMRT is the preferred external beam technique and the regime of 30 Gy in 5 nonconsecutive once-daily fractions is an option for APBI.

Risk-adapted decision-making of postoperative RT

Increasing evidence of precision medicine in personalizing systemic therapy decisions has a growing part in the CSCO BC guideline. Tailoring RT decisions based on clinical and classical histo-pathological parameters and multi-gene expression is the trend towards a precision era of modern RT. Precision medicine is most likely to assist in omitting post-operative RT in low-risk patients after BCS without compromising therapeutic outcome. The updated 7.3-year follow-up of the PRIME II trial once again confirmed the non-inferiority of avoiding postoperative RT in low-risk elderly patients after BCS compared with standard treatment of WBI, which was reported in 2020 SABCS. The results showed equivalence in 10-year OS between patients with and without WBI. Supported by this evidence, this year's updated guideline raised the grade of recommendation on omission of postoperative RT from 2 to 1B for selected low-risk elderly patients after BCS. However, the 10-year rate of IBTR was significantly reduced in patients treated with WBI compared to those who avoided postoperative RT (0.9% *vs.* 9.8%, P<0.01).

As the local control benefit of WBI remains solid, even in those low-risk elderly patients, it is emphasized that omission of RT with its associated risks/benefit assessment should be fully discussed with patients and their families. Newer clinical trials have moved towards investigating selective WBI omission based on the integration of clinical features (patient- and disease-related) and biomarkers with or without gene-signatures are ongoing, such as the IDEA trial (NCT02400190), PRECISION trial (NCT02653755), EXPERT trial, LUMINA trial, PRIMITIME trial, TOP-1 trial, and NATURAL trial. The panel members would like the results from these trials to help oncologists to identify a subset of patients more precisely at very low risk to be safely omitted from postoperative RT after BCS. Another field that novel biomarkers and multigene prognostic modeling would be likely to help is the personalization of RNI in patients with 1–3 positive lymph nodes and favorable clinical/biological factors, prognostic factors, or those with negative lymph nodes but unfavorable clinical/biological factors. There are ongoing international multi-center trial (NCT03488693) or multi-center Chinese trial (NCT04069884). The panel members encourage oncologists to conduct or participate in trials to evaluate the role of RNI with comprehensive biological information along with modern RT techniques.

Evaluation criteria of postoperative RT technical details

The QA quality is essential to exploit the advantages of the IMRT technique in uniform dose coverage of target volume and protecting normal tissues in clinical practice, especially when a high fractionated dose is adopted. However, details of QA requirements are usually lacking in the traditional breast cancer clinical practice guidelines. In this year's updated guideline, a recommendation is given on evaluation criteria of dose volume histogram (DVH) constraints of organs-at-risk (OARs) and planning treatment volume (PTV) dose distribution for the 1-week regime of HF-WBI by referring to the protocol of FAST-FORWARD trial. The evaluation criteria were detailed as following: D95% of PTV >95% prescription dose, D5% of PTV <105% prescription dose, D2% of PTV <107% prescription dose, maximum dose of PTV <110% prescription dose; V8Gy of ipsilateral lung <15%; and V1.5Gy of heart <30 %, V7Gy of heart <5%. The panel members hope that the details of QA requirements will promote the safe and effective implementation of the 1-week regimen of WBI in routine clinical practice.

Conclusions

Updates in postoperative RT in the new version of the CSCO BC guideline for 2021 can be summarized as follows: (I) prioritize the routine clinical practice of HF regime in postoperative RT, especially in BCS patients receiving WBI without RNI; (II) refine risk-adapted decision-making of RT; (III) recommend comprehensive criteria of postoperative RT technical details. All the updates are based on new evidence from clinical trials published or issued over the past year. The panel members will continue to update the guidelines, translate the latest and important research into clinical practice, especially in those "grey and debatable zones" of postoperative RT.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tbcr-21-15). ZJ serves as an Editor-in-Chief of *Translational Breast Cancer Research*. JC serves as an unpaid editorial board member of *Translational Breast Cancer Research*. The other authors have no conflicts of interest to declare.

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