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Clinical practice guideline for breast-conserving surgery in patients with early-stage breast cancer: Chinese Society of Breast Surgery (CSBrS) practice guidelines 2021

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Breast-conserving surgery (BCS) with radiotherapy is the primarily agreed surgical choice for eligible patients with an early diagnosis of breast cancer. In 2019, the panel of Chinese experts assembled by the Chinese Society for Breast Surgery (CSBrS) developed a Chinese experts' consensus on BCS for early-stage breast cancer (Version 2019) with the aim of standardizing BCS in China. Subsequently, the CSBrS conducted a review of published reports and discussions between experts to determine the key clinical questions for the Clinical Practice Guideline for BCS in Patients with Early-Stage Breast Cancer. The group evaluated the relevant evidence using the grading of recommendations assessment, development, and evaluation system, and developed a Clinical Practice Guideline for BCS in Patients with Early-Stage Breast Cancer (Version 2021), with the aim of providing guidance on clinical practice to breast surgeons in China.

Level of Evidence and Recommendation Strength

Level of evidence standard[1]

Recommendation strength standard[1]

Recommendation strength review committee

The panel for this guideline is comprised of 85 experts, including 70 (82.3%) breast surgeons, four (4.7%) medical oncologists, four (4.7%) diagnostic radiologists, two (2.4%) pathologists, one (1.2%) obstetrician, two (2.4%) radiation oncologists, and two (2.4%) epidemiologists.

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Target Audience

Clinicians specializing in breast diseases in China.

Recommendations

Recommendation 1: Indications (all of the indications should be met).

No.	Indications	Level of evidence	Recommended strength
1.1	Patient wishes to preserve her breast	I[2,3]	A
1.2	Clinical Stage I, II, or ≤cT2	I[2-5]	A
1.3	Able to achieve acceptable cosmetic outcomes after BCS	I[2,3]	A

Recommendation 2: Contraindications (any one of the indications is sufficient).

No.	Contraindications	Level of evidence	Recommended strength
2.1	Cannot receive radiotherapy after BCS	I[4,6]	A
2.2	Unable to achieve negative surgical margins	I[2,3,7-9]	A
2.3	Extensive microcalcification	I[2,3,8]	A
2.4	Inflammatory breast cancer	I[2,3]	A
2.5	Patient refusal to undergo BCS	I[2,3]	A

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Recommendation 3: Surgery.

No.	Surgeries	Level of evidence	Recommended strength
3.1	Incorporation of oncoplastic techniques is able to improve the cosmetic outcomes after BCS	II[9-11]	A
3.2	It is recommended that inert metal clips (eg, titanium clips) be placed in the surgical bed after BCS as a localization marker for radiation boosting	I[2,3]	A

Recommendation 4: Pathology.

No.	Pathologies	Level of evidence	Recommended strength
4.1	Margin assessment after BCS is mandatory	I[2,3,8]	A
4.2	Intraoperative frozen section analysis for margin assessment is recommended	I[2,3,12]	A
4.3	Post-operative formalin-fixed, paraffin-embedded tissue analysis is recommended for margin assessment	I[2,3,8]	A
4.4	Methods for margin assessment:		
	Lumpectomy margin assessment (perpendicular inked method)	I[2,4,13]	A
	Lumpectomy margin assessment (tangential shaved method)	II[2,14]	A
	Cavity wall (tumor bed) sampling	II[3,15-21]	A

Recommendation 5: Radiotherapy.

No.	Radiotherapy	Level of evidence	Recommended strength
5.1	Whole-breast irradiation is recommended after BCS*	I[2,4,6]	A

* Whole-breast irradiation can be waived in patients aged >65 years with Stage I breast cancer, hormone receptor-positive tumors, and negative surgical margins (CALGB9343 trial).

Discussion

A considerable amount of evidence from the scientific literature supports the safety and efficacy of combining BCS with radiotherapy in the early stages of breast cancer. In the National Surgical Adjuvant Breast and Bowel Project B-06 trial, a total of 1851 patients diagnosed with Stage I or II breast cancer were randomly allocated to three study arms, namely total mastectomy, BCS, and BCS with radiotherapy. According to results of the long-term follow-up that lasted 20 years, it was found that disease-free survival, metastasis-free survival, and overall survival did not differ significantly between the three arms.[4] During the same period, in the Milan I trial, seven hundred and one patients with <T2 breast cancers (tumor size measuring <2 cm) were randomized to two arms: radical mastectomy and BCS with radiotherapy. The 20-year follow-up results indicated that there was no significant difference between the overall survival of the two arms. However, the cumulative recurrence rate was higher in the BCS + radiation arm (8.8%) when compared with the mastectomy arm (2.3%).[5] A short-term follow-up study of 95 Chinese patients by Li *et al*[22] revealed that, after an average follow-up of 17 months, the 2-year local recurrence rate of Stage I or II breast cancer after BCS was only 1.4%, with no metastases or deaths. Chen *et al*[16] used propensity-score matching to compare the clinical outcomes after a median follow-up of 67 months of 2866 patients with early-stage breast cancer who had undergone BCS or mastectomy in China; they confirmed the safety and efficacy of BCS. Recently, BCS has been recommended internationally as the standard surgical treatment for eligible breast cancer patients in the early stages.[2,3,8] The panel members agreed that, provided acceptable cosmetic outcomes could be expected, BCS is suitable for patients with clinical Stage I or II disease or ≤T2 tumors who wish to preserve their breasts.

The result of Early Breast Cancer Trialists' Collaborative Group meta-analysis revealed that neoadjuvant chemotherapy can significantly increase the BCS rate. The 10-year cumulative local recurrence rate was slightly, but not significantly, higher in the neoadjuvant chemotherapy than in the untreated group (15.1% *vs.* 11.9%, $P = 0.10$). No significant differences were observed in the 10-year cumulative rates of breast cancer-related deaths between patients who did and did not receive neoadjuvant chemotherapy (27.5% *vs.* 24.8%, $P = 0.15$).[23] Therefore, for patients who were clinically diagnosed with Stage III breast cancer or >T2 tumors, it is possible to administer neoadjuvant chemotherapy to downstage the tumor, and thus increase the chances of being eligible for BCS. The panel members considered that, in clinical practice, it is not always easy to accurately measure the degree of shrinkage of a tumor after neoadjuvant chemotherapy. Thus, there was a lack of consensus in the panel regarding the optimal extent of surgery in patients with breast cancer who have received neoadjuvant chemotherapy. However, there was agreement that achieving negative surgical margins is mandatory in this situation.

The panel considered that the following factors are potential risk factors for local recurrence after BCS: breast cancer located in the central portion; bloody discharge from the nipple; large tumor (eg, >T2); multifocal breast cancer; multicentric breast cancer; young age (<35 years); and radiotherapy contraindicated (eg, active connective tissue disease). However, there is no high level evidence that the abovementioned factors are contraindications to BCS.

Achieving negative surgical margins is mandatory for successful BCS. There is evidence that positive surgical margins are closely associated with local recurrence.[2,8,9,24] Intra-operative gross inspection,[25] imprint cytology,[26] intra-operative specimen imaging,[27] and novel devices[28,29] can also reportedly reduce the rates of positive margins. However, the panel does not recommend these approaches because of the lack of high-level evidence. Intra-operative frozen section analysis (FSA) is reportedly capable of reducing the rates of margin positivity and second surgeries.[30] The panel considers that FSA is widely

used in clinical practice in China and supports its use for intra-operative margin assessment. The panel take a cautious attitude toward performing margin assessment only by post-operative formalin-fixed, paraffin-embedded examination.

Both lumpectomy margins and cavity margins are suitable for the margin assessment of BCS. Lumpectomy margins are assessed on the surface of the tumor-containing specimen. There are two techniques that can be used for margin assessment: the perpendicular inked and tangential shaved techniques.[2,14] Cavity margins are assessed by performing a biopsy (tissue sampling) of the residual cavity (or the wall of the tumor bed) after tumor removal. Well-designed studies suggesting that cavity margin assessment alone is capable of achieving excellent local control have been published.[15,19]

A meta-analysis has demonstrated that the "no-ink on tumor" is significantly associated with a reduced local recurrence rate and that wider surgical margins do not further improve the local control rate.[31] Furthermore, the increased risk of local recurrence associated with positive surgical margins is not nullified by post-operative radiotherapy. There is no evidence that different margin widths should be considered for patients of different ages or with different molecular subtypes. A real-world study (CSBrS-005) conducted by the CSBrS in 2019 revealed that 88.2% (1530/1734) of patients who had undergone BCS had margin widths >5 mm.[32] Others have reached consensus on diagnosing negative surgical margins for infiltrating ductal carcinoma and ductal carcinoma *in situ* by "no-ink on tumor" and "≥2 mm," respectively.[2,3,7] The panel considered these standards inappropriate for China and has not recommended them for routine use.

The panel agreed that whole-breast irradiation (RT) is necessary after BCS. However, the CALGB9493 trial showed a small improvement of locoregional recurrence rate in BCS patients who received RT (RT: 2% (95% confidence interval [CI]: 1% to 4%) vs. no-RT: 10% (95% CI: 7% to 15%)), but no statistically significant differences in 10-year distant metastasis and overall survival between patients with low-risk BCS who did and did not undergo RT. [33] In contrast, the PRIME II trial showed that, in patients aged ≥65 years with early-stage and hormone receptor-positive disease who underwent BCS, the 5-year ipsilateral recurrence rates were 4.1% and 1.3% ($P = 0.0002$) in the no-RT and RT groups, respectively.[34] Although this difference is statistically significant, the benefit is not clinically important. The panel suggested that RT might be forgone after BCS in certain situations related to the patients' preferences and comorbidities.

The International Breast Cancer Study Group VI-VII trial[35] aimed to analyze how the timing of RT affects the local failure rate and disease-free survival (DFS) in breast cancer patients. Among pre/perimenopausal patients, the 15-year DFSs were 48.2% *vs.* 44.9% (hazard ratio [HR] = 1.12, 95% CI: 0.87–1.45) in patients allocated 3 and 6 months of initial chemotherapy (CT). Among post-menopausal patients, the 15-year DFS was 46.1% and 43.3% in the group that did not receive CT initially and the group allocated 3 months of CT, respectively (HR 1.11, 95% CI: 0.82–1.51). The results of this clinical trial suggest that delaying RT until after completion of CT is safe and reasonable. The panel recommended that whole-breast RT is indicated for eligible breast cancer patients after BCS and CT.

The CO-HO-RT trial[36] revealed that the risk of developing grade ≥2 radiation-induced subcutaneous fibrosis is similar in patients who receive concurrent *vs.* sequential RT and endocrine therapy, suggesting that concurrent use of these treatment modalities is safe. According to the 3.7-year follow-up data of the N9831 trial,[37] concurrent use of RT and trastuzumab did not significantly increase cardiotoxicity, supporting the feasibility of the concurrent use of RT and anti- human epidermal growth factor receptor 2 (HER2) treatments. The panel recommended the concurrent use of RT and endocrine therapy, as well as anti-HER2 therapy if indicated.

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Conflicts of interest

The expert committee for these guidelines declares no conflict of interest.

These guidelines are a reference for breast disease specialists in clinical practice. However, the guidelines are not to be used as the basis for medical evaluation, and do not play an arbitrating role in the handling of any medical disputes. The guidelines are not a reference for patients or non-breast specialists. The Chinese Society of Breast Surgery assumes no responsibility for results involving the inappropriate application of these guidelines, and reserves the right to interpret and revise the guidelines.

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