

Peer Review File

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**Reviewer A**

A wonderful team effort putting together these guidelines for the management of bone health in early breast cancer, especially as breast cancer patients are leaning towards survivorship issues given that they are living longer, and being diagnosed earlier. Hopefully this article will help standardise management in China, but also one that can be used internationally as well. A few grammatical issues, but otherwise no major concerns with content. Please see below.

Abstract

1. Revise the sentence - As the overall survival of patients with early breast cancer continues to increase, bone health outcomes require extensive attention

Comment 1: Revise the sentence - As the overall survival of patients with early breast cancer continues to increase, bone health outcomes require extensive attention.

Reply 1: We have modified this sentence as advised.

2. Revise the phrase - Based on the guidelineS and the substantial evidence-based medicine (EBM),

Comment 2: Revise the phrase - Based on the guidelineS and the substantial evidence-based medicine (EBM),

Reply 2: We have changed as suggested.

3. Revise the phrase - in order to further standardize the management of patients' bone health

Comment 3: Revise the phrase - in order to further standardize the management of patients' bone health

Reply 3: We have modified this sentence as advised.

Paragraph 1

1. First sentence revise - Breast cancer has become one of the most common malignant tumors in China and WORLDWIDE

Comment 1: First sentence revise - Breast cancer has become one of the most common malignant tumors in China and WORLDWIDE

Reply 1: We have modified this sentence as advised.

2. Second sentence – “the latest DATA” (not date)

Comment 2: Second sentence – “the latest DATA” (not date)

Reply 2: the latest date (2020)

3. Please alter the sentence - With early breast cancer patients living longer and achieving prolongation in metastasis free survival, survivorship concerns, especially with regards to bone health has attracted more and more attention.

Comment 3: Please alter the sentence - With early breast cancer patients living longer and achieving prolongation in metastasis free survival, survivorship concerns, especially with regards to bone health has attracted more and more attention.

Reply 3: We have modified this sentence as advised.

### Background 1.1

1. Second paragraph first and second sentence – Recognition and diagnosis of CTIBL requires active decision making by clinicians, with notably, age and treatment of breast cancer patients can lead to CTIBL.

Third sentence - Fracture caused by CTIBL HAS BEEN DEMONSTRATED TO significantly reduce the quality of life and survival of BC patients

Last sentence - Therefore, a routine assessment of the bone health for these patients should be PERFORMED by clinicians.

Comment 1: Second paragraph first and second sentence – Recognition and diagnosis of CTIBL requires active decision making by clinicians, with notably, age and treatment of breast cancer patients can lead to CTIBL.

Third sentence - Fracture caused by CTIBL HAS BEEN DEMONSTRATED TO significantly reduce the quality of life and survival of BC patients

Last sentence - Therefore, a routine assessment of the bone health for these patients should be PERFORMED by clinicians.

Reply 1: We have modified this sentence as advised.

2. Third paragraph – revise punctuation with commas and spaces. First sentence= revise - Endocrine therapy is the CORNERSTONE of adjuvant therapy for patients with hormone receptor positive (HR+) breast cancer, but one of the key side effects of endocrine therapy due to oestrogen depletion is the occurrence of osteoporosis and fractures(5).

- Change post menopausal people to post menopausal WOMEN.

Comment 2: Third paragraph – revise punctuation with commas and spaces. First sentence= revise - Endocrine therapy is the CORNERSTONE of adjuvant therapy for patients with hormone receptor positive (HR+) breast cancer, but one of the key side effects of endocrine therapy due to oestrogen depletion is the occurrence of osteoporosis and fractures(5).

- Change post menopausal people to post menopausal WOMEN.

Reply 2: We have modified as advised.

#### 1.2.1.1 Related factors of breast cancer treatment

Needs a bit of summarisation as it's a bit repetitive about the advantages (benefits of HR+ treatment) and disadvantages (bone loss) of oestrogen depleting therapy.

#### 1.2.1.2 Other basic diseases

Can reference - Mann GB, Kang YC, Brand C, Ebeling PR, Miller JA. Secondary causes of low bone mass in patients with breast cancer: a need for greater vigilance. J Clin Oncol. 2009;27:3605-3610.

Or

Grossmann M, Ramchand SK, Milat F, Vincent A, Lim E, Kotowicz MA, Hicks J, Teede H. Assessment and management of bone health in women with oestrogen receptor-positive breast cancer receiving endocrine therapy: Position statement of the Endocrine Society of Australia, the Australian and New Zealand Bone & Mineral Society, the Australasian Menopause Society and the Clinical Oncology Society of Australia. Clin Endocrinol (Oxf). 2018 Sep;89(3):280-296. doi: 10.1111/cen.13735. Epub 2018 Jun 14. PMID: 29741296.

About % of patients in early breast cancer who have found to have underlying low BMD

#### 1.2.2.1 BMD Monitor

- Typical acronym for Dual energy Xray absorptiometry is DEXA

Comment 1: 1.2.2.1 BMD Monitor

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Reply 1: We have modified as advised.

#### 1.2.2.2 CTIBL risk classification and fracture risk assessment

Edit first sentence - American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) bone health guidelines IN CONTEXT OF EARLY BREAST CANCER PATIENTS recommend that POSTMENOPAUSAL AND ELDERLY BREAST cancer patients, post chemotherapy, endocrine therapy and post oophorectomy patients should monitor BMD routinely

Chinese expert consensus – edit no iii

iii. T value < -1.0 and exists any two OSTEOPOROSIS RISK FACTORS at the same time(degree of consensus:96%).

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Reply 1: We have modified as advised.

#### 1.3.1 Lifestyle improvement – grammatical errors

First few sentences - The risk of osteoporosis HAS BEEN DEMONSTRATED TO increase by smoking, and ALSO decrease after SMOKING CESSATION. IN ADDITION, ALCOHOL CONSUMPTION CAN AFFECT BMD, AND THUS LIFESTYLE RECOMMENDATIONS WOULD BE SMOKING CESSATION AND ALCOHOL IN MODERATION.

“Regular moderate weight-BEARING exercise MAY BENEFIT BMD IMPROVEMENT”

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“Regular moderate weight-BEARING exercise MAY BENEFIT BMD IMPROVEMENT”

Reply 1: We have modified as advised.

1.3.3 – The second paragraph is not necessary as have already discussed the benefits and disadvantages of adjuvant endocrine therapy in 1.2.1.1 (repetitive)

Comment 1: 1.3.3 – The second paragraph is not necessary as have already discussed the benefits and disadvantages of adjuvant endocrine therapy in 1.2.1.1 (repetitive).

Reply 1: We have modified as advised.

#### 1.3.3.2

First paragraph – EDIT SENTENCE

Routine monitoring of BMD is not required unless the patients being affected by ADDITIONAL OSTEOPOROTIC additional osteoporotic risk factors.

Comment 1: First paragraph – EDIT SENTENCE

Routine monitoring of BMD is not required unless the patients being affected by

ADDITIONAL OSTEOPOROTIC risk factors.

Reply 1: We have modified as advised.

In 2. Prevention of bone metastases in early breast cancer

- Would be good to write about the impact bone mets have on breast cancer with regards to outcomes of skeletal related events
- For 2.2 – Perhaps a title sentence to the paragraph would be better read as All subtypes of breast cancer (ER+, ER-, HER2 driven cancers and triple negative breast cancers) can all lead to bone metastases. Risk factors for increased rates of bone metastases include.... (currently this paragraph is many listed risk factors which is not clear to the reader how to interpret these)
- For 2.2 – change “isn’t” to is not

Reply 1: We have modified as advised.

Important when discussing the AZURE study (and other adjuvant studies) with regards to the use of adjuvant bisphosphonates to prevent bone metastasis, is to note that there is no overall survival benefit. But despite no OS benefit, it is important to decrease bone mets due to skeletal related events (and thus this needs to be defined and discussed)

Would be good to include the adverse effects of zoledronic acid and contraindications. Whilst osteonecrosis of the jaw is noted, also need to mention not to be used in hypocalcaemia and chronic kidney disease. Given the consensus guidelines – would be good to note if kidney function, calcium or vitamin D check is required before prescribing zoledronic acid (noted dental review is reported)

### **Reviewer B**

Bone health management is an important part of the case management of breast cancer. This expert consensus is about management of bone health in female patients with early breast cancer in China. The manuscript is clearly structured and the key message is to some extent comprehensive. But according to the view of evidence-based medicine, the manuscript still needs some revision.

Please see the comments below.

Comment 1 : Is the consensus formulation following the GRADE guideline (the Grading of Recommendation Assessment , Development and Evaluation) ?

Reply1 : Yes, the consensus formulation is following the GRADE guideline.

Comment 2 : All the experts of the manuscript should declare conflicts of interest to

ensure the independence and impartiality of expert consensus.

Reply 2 : All authors declared no conflicts of interest.

Comment 3 : Expert consensus should include a section describing the contribution made by each author to the manuscript. And the method and process of consensus making should be described in detail.

Reply 3 : The Society of Breast Cancer of China Anti-Cancer Association and the Breast Cancer Study Group Along Yangtze River organized experts from breast surgery, oncology, and other related departments across the country to establish a consensus expert group. Referring to domestic and foreign guidelines, consensus and evidence-based medical evidence, combined with clinical experience, targeted discussion, and voting to reach a consensus, the members of the expert group developed the Chinese expert consensus recommendations for management of bone health in female patients with early breast cancer (2022 edition).

Comment 4 : According to the “Guidelines for Authors”, the abstract is suggested for 200~350 words structured with the subheadings Background, Methods, Results, and Conclusions.

Reply 4 : Background: The management of bone health in female patients with early breast cancer includes managing bone loss and preventing bone metastasis. As the overall survival of patients with early breast cancer continues to increase, bone health is getting extensive attention. However, there is no specific consensus in China on the methods and strategies of management and treatment. Methods & Conclusions: Based on the guideline and the substantial evidence-based medicine (EBM), the Society of Breast Cancer of China Anti-Cancer Association and Breast Cancer Study Group Along Yangtze River thoroughly discussed and formulated the Chinese expert consensus recommendations for management of bone health in female patients with early breast cancer (2022 edition), in order to further standardize the management of patient's bone health.

Comment 5 : The conclusion should be added to the end of the manuscript.

Reply 5 : The end of every part adds to a conclusion, so the conclusion is not added to the end of the manuscript.