

Peer Review File

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Reviewer comments

Introduction

First Paragraph (lines 63 to 74)

Consider clarifying that you are talking about primary surgery.

Reply: This has now been clarified and the term “upfront surgery” has been added. (Page 4, lines 62-63).

Changes in the text: Sentinel lymph node biopsy (SLNB) at upfront surgery is the gold-standard surgical method for axillary lymph node staging in early stage breast cancer.

Consider changing order: explain first the validation of the SLNB procedure and then its effects on morbidity and overall and disease-free survival despite differences in false negatives rates.

Reply: The order has now been changed, with the following sentence now placed at the end of the first paragraph. (Page 4, lines 72-74).

Changes in the text: Nevertheless, the technique has the advantages of reducing surgical morbidity with no negative effect on prognosis (4-7).

Review reference 7 (Mansel RE, ... Randomized multicenter trial...). Reference 7 talks about quality of life, not false negative rate.

Reply: Thank you for pointing this out. The order of the references has now been changed. (Page 4, 71-74).

Changes in the text: The false-negative rate in some analyses, however, exceeded the value considered ideal in previous studies (4.6–9.8%) (4-6). Nevertheless, the technique has the advantages of reducing surgical morbidity with no negative effect on prognosis (4-7).

Second Paragraph (lines 91 to 94)

I would suggest being clearer in the argument to consider sentinel lymph node biopsy after neoadjuvant as:

“Axillary downstaging in responding tumors leads us to consider sentinel lymph node biopsy after NACT to avoid morbidity from complete axillary dissection”.

Reply: **This has now been clarified, and the suggested sentence has been added to the text. (Page 5, lines 93-95).**

Changes in the text: **In this new scenario, axillary downstaging in responding tumors leads us to consider SLNB after NACT to avoid morbidity from complete axillary dissection.**

1. Initially negative axilla (cN0) and SLNB

I would suggest “Clinically negative nodes at diagnosis and SLNB after NACT” –

Reply: **Thank you for this suggestion. The text has been changed accordingly. (Page 6, line 114).**

Changes in the text: ***1. Clinically negative nodes at diagnosis and SLNB after NACT***

Line 123: Consider beginning the sentence with “On the other hand, studies on clinical outcomes...”

Reply: **The text has been changed to include this suggestion. (Page 6, lines 125-126).**

Changes in the text: **On the other hand, studies on clinical outcome are limited to data from non-randomized trials.**

Line 126: Place reference 13 after the results of the study on line 127.

Reply: **The position of reference 13 has been changed in accordance with the reviewer’s suggestion. (Page 6, line 129).**

Changes in the text: **Lymph node recurrence rate was 1.2% in the NACT group and there was no difference in terms of disease-free survival or overall survival (13).**

Line 127: I would suggest explaining GENE-2 study better.

Reply: **A better description of this study has now been provided. (Page 6, lines 129-134).**

Changes in the text: **The GANE-2 study was a prospective multi-institutional French cohort**

study aimed at assessing the accuracy and safety of SNLB after NACT in initially cN0 and pN1 patients. Of the 419 initially cN0 patients treated with SNLB alone, only one patient had lymph node recurrence after a mean follow-up time of 36 months, while patients allocated to the pN1 group underwent SLN dissection (SLND) and axillary dissection (FNR: 11.9%) (14).

Consider reviewing

2. Initially positive axilla (cN1/2) and clinical complete response following NACT

Line 135: “the majority had axillary pathologic response” This is not very accurate.

Approximately 40 % of patients obtain complete pathologic response and differ according to subtypes. –

Reply: We agree with the reviewer and this sentence has been changed accordingly. (Page 7, lines 139-141).

Changes in the text: [...] therefore, all these women were submitted to axillary dissection despite the fact that a considerable number of patients had axillary pathologic complete response (11).

Line 135-139: The studies are listed in this order: Z1071, SENTINA and SN-FNAC. It is necessary to reorder the references.

Reply: The order of the studies in the sentence has been changed to comply with the order of the references. (Page 7, lines 141-144).

Changes in the text: The SENTINA, Z1071 and SN-FNAC studies changed this concept. The overall false-negative rates reported by those studies for patients submitted to NACT were 14.2%, 12.6% and 13.3%, respectively, rates that were higher than that of 10% previously specified as being safe but lower than other previously reported rates (15-17).

Line 152: SENTINA study did not mark the metastatic node at prior.

Reply: Thank you for pointing this out. This sentence has now been removed from Page 7, previously on line 157.

Changes in the text: Sentence removed.

Line 157-158: The sentence “the clipped lymph node was not identified in 23% of patients” is not correct. “Among the 134 patients who underwent SLND, the clipped node was not identified

as an SLN in 23% (31 of 134) of patients” (from Caudle et al.)

Reply: Thank you for pointing this out. The sentence has now been changed accordingly. (Pages 7-8, lines 159-161).

Changes in the text: In a retrospective study conducted at the MD Anderson Cancer Center, of the 134 patients who underwent SLND, the clipped node was not identified as an SLN in 23% (31 of 134) of patients.

Line 159: I would suggest explaining the technique of targeted axillary dissection (TAD) better: when the SLN was marked and located using iodine-125 seeds. TAD includes SLNB and the removal of the clipped node.

Reply: The text has now been altered to clarify the description of this technique. (Page 8, lines 164-168).

Changes in the text: In TAD, patients with a clipped node (biopsy-confirmed nodal metastases) are marked with an I-125 seed. This is performed after undergoing NACT and receiving an injection of mapping agents (radioisotope and/or blue dye) prior to surgery. A gamma probe is then used to identify the seed and the radioisotope-containing nodes removed during surgery, including nodes containing blue dye alone or those found to be palpable (18).

Line 164: It is mandatory to order the references. From reference 18 skip to 38.

Reply: In fact, the references are in the correct order as 37 references are cited in the Introduction, as shown in its last paragraph and highlighted here (Pages 5-6, lines 103-110): *[...] In addition to the lack of randomized studies assessing clinical outcomes, overall false-negative rates are considered high, possibly impacting on local control and important prognostic information (15-23). More recently, there has been an increasing tendency to omit axillary dissection in patients with a positive SLNB (ypN+) following NACT, as in cases of upfront surgery in circumstances similar to those of the Z11 study, even when the residual burden is high (24-29). Another line of investigation has evaluated the consequences of omitting any axillary surgery in patients who respond well to NACT (30-37). The objective of the present paper is [...].* (Page 6, line 110).

Changes in the text: Changes do not apply.

Line 188-193: Consider not issuing your opinion in this section.

Reply: **As suggested by the reviewer, this sentence has been duly changed. (Page 9, lines 195-200).**

Changes in the text: **The search for a lower false-negative rate remains most relevant, since, even if there is no locoregional effect of a higher false-negative rate, identifying a residual lesion could be crucial when deciding on whether to use systemic adjuvant therapy with capecitabine for triple-negative tumors or olaparib for patients with the BRCA mutations and trastuzumab emtansine (T-DM1) in HER2 disease.**

After reading this part I suggest reconsider the title: when you write “clinical complete response”, I understand you are referring to pathologic response in the sentinel nodes.

Title, would it be: Initially positive axilla (cN1/2) and negative SLNB following NACT?

Reply: **The title of this section has now been changed as suggested. (Page 7, line 136).**

Changes in the text: ***2. Initially positive axilla (cN1/2) and negative SLNB following NACT***

–I would consider it necessary to reword this section:

- To explain targeted axillary therapy more clearly - and to specify whether the studies referred to in terms of axillary recurrence refer to negative sentinel node results regardless of the strategies used to reduce false negatives.

Reply: **The description of TAD has been improved. (Page 8, lines 164-168).**

Changes in the text: **In TAD, patients with a clipped node (biopsy-confirmed nodal metastases) are marked with an I-125 seed. This is performed after undergoing NACT and receiving an injection of mapping agents (radioisotope and/or blue dye) prior to surgery. A gamma probe is then used to identify the seed and the radioisotope-containing nodes removed during surgery, including nodes containing blue dye alone or those found to be palpable (18).**

3. Positive SLN following NACT

Reorder the references.

Reply: **In fact, the references are in the correct order. In the previous ‘section 2’, citations go up to number 43 (Page 9, line 195) and in ‘section 3’, citations start at number 44 (Page 9, line 205). After that, citations continue, arranged in increasingly numerical order throughout the text.**

Changes in the text: **Changes do not apply.**

I would suggest focusing on the differences in terms of axillary residual disease after sentinel node between primary surgery and NACT. Explain better references 26 to 28.

Reply: **A sentence has been added comparing NACT with upfront surgery (27% additional disease on Z11 trial). (Page 10, lines 212-215).**

Changes in the text: **Single center analyses have shown high residual cancer burden in around 60% of cases after NACT irrespective of the extent of metastasis (micro- or macro-metastasis) or of the subtype of the disease (26-28). This rate compares with the rate of 27% found in the Z11 trial and 13% for micro-metastasis alone (IBCSG 23-01) at upfront surgery (44,49).**

4. Omitting axillary surgery in good responders

Lines 284-285: Consider being clearer in the abbreviations of tumor subtypes

Perhaps it would be more didactic to comment on this section by differentiating between the two possible settings: clinical node negative or positive at diagnosis.

Reply: **The abbreviations of tumor subtypes have now been clarified, as suggested. (Page 13, lines 295-298).**

Changes in the text: **Residual disease in axillary lymph nodes was found in 1.0%, 1.6%, 2.1% and 4% of cases of HER2-positive/HR-negative, triple-negative (HER2-negative/HR-negative), HER2-positive/HR-positive and HR-positive/HER2-negative tumors, respectively (30).**