Peer Review File

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Reviewer comments

Reviewer A

Comment 1: Interesting discussion on a relevant topic. However, I feel that this review could do with more impact. Each paragraph is just stating facts and listing key trials in each sub topic, but without any views/critique from the authors. So how does this review guide the surgeon? Should DCIS be treated conservatively? For the non-surgeon, is there still a role in testing the IHC/hormonal receptors for DCIS? There are quite a few recent papers on this. It is still divided if hormonal receptors should be routinely tested, and whether hormonal therapy should be offered. Are there differing outcomes in ER+ and ER- DCIS? Between the low-grade and high-grade DCIS? The authors appear to discuss a lot on anti-HER2 therapy for DCIS. Whilst it is a new field, is this really less aggressive than surgery? It seems far more expensive and more aggressive a treatment. But this is my view. Would like to hear the authors' opinion.

Reply 1: For this review, I included key papers that define management of DCIS. I wanted to start with background about DCIS, including contrasting it with invasive breast cancer. Receptor status is important for DCIS management and helps determine adjuvant treatment, as outlined in NCCN guidelines. I included the anti-HER2 treatment as this is something that is on the horizon and could change our management of DCIS. I think we will have to see if it will be too expensive or aggressive for patients, but I see your point. What I wanted to emphasize in this study is that DCIS management is moving away from surgical management with RT, which is aggressive and managed similarly to invasive cancer, to less invasive treatment, including endocrine therapy. Most patients with DCIS are currently treated with multimodal therapy as someone with invasive cancer and I think we are moving away from this and making patient care more individualized.

Comment 2: How about pre-operative workup? This could be a separate subtopic on its own, instead of being parked under surgical management.

Reply 2: That is a good point. I will discuss pre-op management and combine it with

the MRI section to make it more cohesive.
Changes in the text: The National Comprehensive Cancer Network's (NCCN), workup for patients with DCIS include a history and physical exam, bilateral diagnostic mammogram, and pathology review of biopsy, including estrogen receptor status (16). Genetic testing is considered for patients who are determined to be at risk for hereditary breast cancer. Breast MRI is indicated, if appropriate. MRI can be used for staging and is more sensitive and accurate compared to mammography in detecting extent of disease, particularly for multifocal or multicentric disease (17, 18).

A meta-analysis of nine retrospective studies on the effect of pre-operative MRI on the surgical management of DCIS found that MRI significantly increased the odds of having an initial mastectomy (OR 1.72, p=0.012) (19). There was no significant difference in the rate of positive margins or re-excision in women who underwent wideexcision as their initial surgery. The meta-analysis concluded that pre-operative MRI did not improve surgical outcomes in women with DCIS.

A non-randomized clinical trial found that in 339 women with DCIS who underwent pre-operative MRI, 19% of patients eligible for wide excision converted to mastectomy (20). Conversions were based on MRI findings (38%), patient preference (38.5%), positive margins attempted wide excision (15.4%), positive genetic test results (4.6%), and contraindication to RT (3.1%). A disadvantage of MRI is that it was associated with additional biopsies in 19.8% of patients. The clinical trial concluded that MRI can be useful in terms of planning management
for DCIS patients.
(see pages 5-6, lines 108-128)

Comment 3: What were the methods used in this review to search for papers related to this topic?
And are the authors' expert opinion on this ever changing and controversial topic. Conclusion is short.
Reply 3: I did not have any analytical method in choosing the papers, but specifically chose key papers that influence the management of DCIS. I have also included important guidelines, such as from NCCN and ASTRO, that are routinely referenced

when treating patients. I will elaborate the conclusion and include my opinion on future management, but I want the reader to come to their own conclusions as well since there are many controversies in breast management and often times, no right or wrong answer.
Changes in the text: Primary care providers and general surgeons, as well as, of course, surgeons specializing in breast care, will encounter patients diagnosed with DCIS. It usually appears as a group of calcifications on mammography, at which point core needle biopsy is recommended. Once diagnosed, the patient should be referred to a surgeon, if not already. Since it is in situ disease, it is classified as Stage 0 breast cancer. Prognosis is excellent. There is a risk of upstaging to invasive disease, however, on final pathology. Currently, DCIS is managed similarly as invasive carcinoma with multimodal therapy due to this potential risk of progression. Most patients are candidates for BCT, which consists of a lumpectomy and RT. Depending on hormone receptor status, patients may also receive adjuvant endocrine therapy. DCIS has the potential for over treatment due to potentially low risk of upstaging and low mortality rates. The COMET, LORIS, and LORD clinical trials are currently investigating if management can be deescalated. The goal of these trials is to identify low risk DCIS patients who can be safely managed with active surveillance by mammography. I hypothesize, based on prior studies, that the low risk patients will likely have low grade DCIS and be hormone receptor positive while high risk patients will have high grade DCIS and be hormone receptor negative. I predict that management of DCIS will become less aggressive (Figure 2). Neoadjuvant endocrine therapy is currently being investigated and may become routinely administered in hormone receptor positive patients. Anti-Her2 therapy and immunotherapy, which are not standard of care, but may shift the paradigm of DCIS management, too. As we continue to learn more about DCIS, it's management will continue to evolve and the future is promising for individualized therapy tailored to patients. (pages 18-19, lines 445-464)

Comment 4: And a few more minor comments:
Line 29 'usually' appears as a group of calcification.
Reply 4: I agree. I will add 'usually.'
Changes in the text: It is diagnosed with increasing frequency due to widespread screening mammography and usually appears as a group of calcifications. (page 2, lines

29-30)

Comment 5: Line 56 it 'usually' appears as a grouping of calcifations.
Reply 5: I agree. I will add ‘usually.’
Changes in the text: It usually appears as a group of calcifications on mammogram, in which a core needle biopsy is recommended. (page 3, lines 55-56)

Comment 6: Lines 87-89. This sentence is very confusing. What are these percentages trying to tell us? The % who had surgery? who had cancer? who had recurrence?
Reply 6: I agree- the sentence is confusing and I am removing it because I think the point of the sentence does not contribute to the paper. I am deleting that sentence and revising that paragraph (see next point)
Changes in the text: n/a

Comment 7: lines 92-93: Patients who had RT or ET had a reduced risk of ipsilateral recurrence. how about RT + ET? Did this study divide the ER+ and ER- DCIS?
Reply 7: For your first question, I revised the sentence to include statistical analysis to clarify the reduction in ipsilateral recurrence. The study did not divide ER+ and ER- patients.
Changes in the text: The UK Sloane Project is a prospective cohort study of 9,938 women diagnosed with
screen-detected DCIS from 2003 to 2012 (13). 70% of women were treated with breast conserving therapy (BCT) and 30% with mastectomy. Of the patients who underwent RT after lumpectomy, there was a 3.1% absolute reduction in ipsilateral recurrent DCIS or invasive breast cancer. ET was prescribed to more patients after lumpectomy (14%) than mastectomy (8%) ($p<0.001$). Adjuvant ET was associated with a reduction in ipsilateral recurrence whether RT was received (hazard ratio [HR] 0.57; 95% confidence interval [CI] 0.41-0.80) or not (HR 0.68; 95% CI 0.51-0.91) after lumpectomy.
(page 4, lines 84-91)

Comment 8: lines 142-145: Why patients with mastectomy + reconstruction are more

likely to be dissatisfied; and yet, >80% of women who had mastectomy were satisfied with their construction decision. Mastecomy without reconstruction: highest levels of satisfaction. Please help phrase these findings in an easier to read flow.

Reply 8: I agree. The statement doesn't make sense so I clarified that entire paragraph. Changes in the text: A cohort study from 1997 to 2006 surveyed 1,537 women with DCIS about satisfaction with their surgical and reconstruction decisions (27). Over 90% of women were reportedly satisfied with their surgery regardless of the type. Women who underwent mastectomy with reconstruction were more likely to report lower levels of satisfaction than women undergoing BCT (odds ratio 2.98, $p<0.01$), but over 80% of women who underwent mastectomy with reconstruction reported satisfaction with their surgical decision. Women who underwent mastectomy without reconstruction had the highest levels of satisfaction while women with implants were more likely to be dissatisfied. The study concluded that most women were satisfied with their surgical decision. (page 7, lines 165-173).

Comment 9: lines 161 - 178 can be organized to another heading, such as pre-operative workup/investigation. May want to include other modalities of imaging, such as CESM (contrast enhance spectral mammography) and contrasted ultrasound.

Reply 9: I edited that paragraph and moved it into the section about pre-op work up. Changes in the text: The National Comprehensive Cancer Network's (NCCN), workup for patients with DCIS include a history and physical exam, bilateral diagnostic mammogram, and pathology review of biopsy, including estrogen receptor status (16). Genetic testing is considered for patients who are determined to be at risk for hereditary breast cancer. Breast MRI is indicated, if appropriate. MRI can be used for staging and is more sensitive and accurate compared to mammography in detecting extent of disease, particularly for multifocal or multicentric disease (17, 18).

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did not improve surgical outcomes in women with DCIS.

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Comment 10: lines 189-190: 'RT can improve survival in select patients with DCIS' - please define who this select group is.
Reply 10: I should have clarified that; the select group were higher grade, younger, and had a larger tumor size and I edited the sentence to reflect that.
Changes in the text: This significant improvement in survival was only seen in women who were higher grade, younger and had a larger tumor size.
(page 8, lines 192-193)

Reviewer B
This is a well-written review of the subject matter. I recommend publications following a few edits/changes:

Comment 1: Page 5. Line 119. Does this sentence refer to surgery vs. expectant management?
Reply 1: The sentence refers to patients managed with surgery compared to those managed without surgery; I will clarify that.
Changes in the text: Although, Sagara et. al analyzed SEER data and found no breast cancer specific survival benefit of surgery with low grade disease compared to patients managed without surgery. (18). There was, however, a
survival benefit of surgery in patients with intermediate or high grade DCIS. The utility of surgery versus active surveillance for DCIS will be discussed in the Future Management section. (see Page 6, lines 139-141).

Comment 2: Page 6. Line 126. “Recommend” should be “recommended”

Reply 2: I agree and will change that.

Changes in the text: A margin of at least 2 mm between the DCIS and ink is recommended in a consensus statement endorsed by the American Society of Clinical Oncology, Society of Surgical Oncology, and American Society for Radiation Oncology (ASTRO) (21). (see page 6, line 147-150)

Comment 3: Page 7. First paragraph. SNB may able be used at the time of BCS when the location of the incision would interfere with SNB performed at a later date.

Reply 3: I agree that the incision can potentially impact SLNB at a later date and I discuss that in terms of a mastectomy being performed, but other than that, I have not performed a SLNB due to my incision and am not aware of studies supporting this.

Changes in the text: n/a

Comment 4: At various locations in the paper, there is a formatting error where "&#39" appears. These should be corrected.

Reply 4: I am sorry about that. I had to transfer the file between computers and convert the file and this formatting error must have developed. When comparing a prior draft, it looks like symbols like ‘ or < were not formatted properly. I will fix that and simplify it so the formatting does not convert the text. Thank you for bringing it to my attention.

Changes in the text: (They are removed and the edited word is highlighted throughout the paper).

Comment 5: Page 9. Line 201. Correct grammar.

Reply 5: I agree. I am deleting “this.”

Changes in the text: Cardiotoxicity is another concern, but the mean heart dose from RT is minimized when patients perform deep inspiration breath holding techniques during RT. (see page 9, lines 203-204)

Comment 6: Page 14. In the discussion of IORT for DCIS, you reference a patient in which only 4 patients had IORT for DCIS. You should reference my paper on IORT for DCIS, attached, and related articles discussed in the paper.

Reply 6: I would love to reference your paper, but I do not have the reviewers' names and your paper attached. I added another study and discussed it in the revision.
Changes in the text: A prospective non-randomized trial analyzed 35 patients with pure DCIS up to 4 cm in maximum diameter who underwent IORT. At median follow up of 36 months (range 2-83 months), the local recurrence rate was 5.7%. 5 patients (14.3%) had positive margins requiring re-excision or mastectomy due to extensive disease. Thus, 91.4% of patients were successfully managed with lumpectomy and IORT alone. (see page 14, lines 344-349)