Peer Review File

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Reviewer A

This is a rather unconventional paper that attempts to examine the surgical treatment of multiple ipsilateral breast cancers (MIBC) from a surgical perspective (I am not familiar with the term multifocal multicentric breast cancer (MFMCBC). The authors have created a narrative that describes how understanding the anatomy, pathology and molecular aspects of these cancers can potentially aid surgical decision making and in particular promote successful breast conservation surgery (BCS) for this group of patients with multiple cancers in one breast for whom mastectomy has traditionally been recommended. The paper is undoubtedly interesting and thought provoking but is essentially a narrative account with many statements that are rarely expanded upon and have questionable scientific underpinning. It is unclear how some aspects of pathology and molecular genetic changes within a 'sick lobe' can be translated in practice into accurate surgical resection with clear margins and an adequate oncological procedure. The authors have alluded to the application of artificial intelligence for determining suitability of MIBC patients for BCS – however, it is not immediately apparent how this would facilitate planning and execution of surgery.

I have concerns about use of the term sick lobe hypothesis and the concept contain therein; breast surgical resection does not respect the anatomical boundaries of the breast and to do so would severely compromise cosmetic outcomes. The authors describe an elliptical resection of multiple tumours but the latter may not necessarily be confined to a single lobe; indeed, multicentric cancers almost certainly will involve more than one lobe and it is difficult to conceive how multiple elliptical resections can be undertaken and the breast reconstituted with volume displacement as opposed to volume replacement techniques. It is almost implied that procedures such as therapeutic mammoplasty are inappropriate and incur unnecessary disruption to breast tissue that may adversely affect clinical outcomes via perturbation of the immune system. There is no reference to the percentage excisional breast volume - >20% usually demands formal partial breast reconstruction.

The authors suggest that BCS was introduced in 1969 but this was the year Veronesi applied to the WHO and indeed his proposal for a trial of BCS was rejected outright the first time. It really was not until a consensus conference in 1990 that BCS was finally acknowledged in the United States as the preferred surgical treatment options for the majority of women with early stage breast cancer. The authors fail to appreciate the evolution of breast surgery. Moreover, they suggest that the MIAMI trial failed in part because many women with MIBC preferred BCS and did not want to be randomized with the possibility of then undergoing mastectomy. The latter remains the mainstay for treatment of MIBC but data to date suggest that with careful selection, rates of conversion to mastectomy and local recurrence rates for surgically successful BCS for MIBC are acceptable. Moreover, there is a trend for maximal surgery these days with many women opting for bilateral mastectomy (and often immediate reconstruction) for small unilateral cancers that would otherwise be suitable for conventional

BCS.

The authors have cited the work of Roland Holland but have not really described the key findings from his detailed anatomical dissections of mastectomy specimens – basically showing that tumour was present more than 2cm from the index lesion in more that 40% of cases. There could be a much better summary of what constitute MIBC – this is a quotation from an article of mine on this topic:

'Multifocal tumours are present in the same quadrant of the breast and separated by distances varying from 5 - 20mm. This would exclude those cancers where the index lesion is surrounded in the immediate vicinity (<5mm) by very small satellite lesions. Multicentric cancers occur in different quadrants of the breast but would include separate foci of tumour separated by distances of 40 – 50mm in a large breast. There is much variation in the reported frequency of multifocal and multicentric tumours resulting from differences in definition and methods of pathological sampling'.

I am surprised there is no mention of the seminal paper by Van Maaren and colleagues from the Netherlands who first presented retrospective (and confounded) evidence that overall survival might be superior for BCS patients compared with those undergoing mastectomy. They have cited the paper by De La Cruz et al. that involves analysis of more that 1,500,000; nonetheless, this remains a contentious issue and it is my understanding at the present time that most women when discussing surgical options are not told that they are likely to live longer if they chose to undergo BCS! The authors refer to ‘compelling evidence’ and this is a key theme in the article.

I notice the PubMed search was for articles published from 1970 – but at this time few patients were having BCS and certainly not for MIBC. The search criteria are vquite broad and the authors fail to mention how many articles appeared after the first search (which was then reviewed for duplication) (please note that about 20% of phyllodes tumours are malignant). I would challenge the claim that early randomized trials of BCS such as NSABP B-06 showed that local recurrence rates were lower for patients receiving lumpectomy and radiotherapy than mastectomy – these earlier trials of BCS actually showed notably higher rates of local recurrence for BCS but overall survival was the same. In recent years, adjuvant treatments have improved and there is greater attention to surgical margins and now rates of ipsilateral breast tumour recurrence (IBTR) following BCS are relatively low (3.5 – 6.5% at 10 years).

I agree that published data indicate that rates of IBTR are similar for MIBC and for unifocal lesions. However, the authors refer to recent articles that predominantly relate to the period 1990 – 2009. There is no mention of margin width in the context of tumour excision – the authors refer to clear margins – are these ‘no tumour on ink’ or wider margins? There should be much clearer information as to whether MIBC are associated or not with higher rates of locoregional or distant disease recurrence. This is another quotation from my article on MIBC:

'There is therefore an emerging theme declaring that BCS is safe for MIBC in selected patients with low rates of IBTR and acceptable cosmesis. This impression is further reinforced by a study comparing the outcomes for multifocal and multicentric cancers with unifocal cancers (stage I – II) following either mastectomy or BCS. Binary logistic regression analysis was used for prognostic evaluation with matched analysis of patients and cumulative incidence curves. At a median follow up of 7.9 years, cumulative 10 years local recurrence rates were similar for MIBC and unifocal cancers undergoing both BCS and mastectomy. Thus multifocality and multicentricity are not significant risk factors for local relapse nor impaired survival (matched analysis of MIBC versus unifocal cancers (p=0.60)). BCS for multifocal or multicentric cancers was confined to patients without an extensive ductal carcinoma in situ component and smaller invasive tumour foci (≤1cm)'.

There is minimal reference in the literature to the 'sick lobe hypothesis' but the authors focus on this quite heavily in the article and indeed this is a central theme. They fail to appreciate that the ductal-lobular system of the breast has a complex pattern of arborization and different ductal systems are intertwined in a 3-dimensional manner (the occurrence of molecular heterogeneity in more distant foci supports this viewpoint as stated by the authors - '….derived from separate ductal-lobular trees with different genetic ancestry'). These ductal-lobular systems are not neatly confined to individual anatomical lobes. I am uncertain how the authors propose to apply this hypothesis of the sick lobe syndrome to surgical resection of multifocal/multicentric cancers. How can the extent of any molecular or genetic alterations within an individual lobe be delineated prior to surgery and be confidently resected without necessitating removal of an excessive amount of breast tissue (the authors refer to molecular changes being used as markers for adequacy of tissue resection). If tissues are morphologically normal, how can molecularly 'primed' tissue be identified pre-operatively and its resection assured? Removal of a single elliptical segment is rather like the old-fashioned quadrantectomy but this has been superceded by modern methods of oncoplastic breast surgery that can resect tumours with wide margins, low rates of IBTR and excellent cosmetic outcomes – albeit often with the need for contralateral surgery if a volume displacement method (e.g. reduction mammoplasty) has been employed rather than volume replacement.

The authors mention neoadjuvant chemotherapy (NACT) and how this can lead to conversion from mastectomy to BCS in up to 75% of cases – this may be the case for phenotype appropriate tumours where the chance of a complete pathological response is up to 60%. However, there is a disparity between rates of response to NACT and adoption of BCS – rates of BCS after NACT are much lower than expected and may actually reflect a desire of patients to undergo mastectomy rather than BCS after NACT – and this will likely be higher for MIBC where radiological imaging may not be able to accurately predict response to NACT. Which patients should get MRI imaging?

Comments in Paragraph 1 Comment 1 from Reviewer A:
I am not familiar with the term multifocal multicentric breast cancer

We thank Reviewer A for the comprehensive critique of our manuscript. We appreciate Reviewer A's opinion on the terminology of multiple ipsilateral breast cancer (MIBC) and this is the main terminology used in our abstract. However, we included the term multifocal multicentric breast cancer (MFMCBC) as this was an alternative form of referring to such tumours in the literature. A Medline search on PubMed on 6 Dec 2022 with the terms 'multiple ipsilateral breast cancer AND breast conservation treatment' (BCT) yielded 66 articles while a search with the terms 'multifocal multicentric breast cancer AND breast conservation treatment' yielded 101 articles. In order to be as inclusive as possible in our review, we used both terms in our search, and therefore in our manuscript as well. We apologise if we have used the term multifocal multicentric breast cancer (MFMCBC) which Reviewer A might not be familiar with. We hope that Reviewer A would be agreeable to allowing us to continue using this term in our manuscript as the quote from his/her article in the review also uses similar terms (please see paragraph 5 of Reviewer A's comments, with emphases being ours): 'Multifocal tumours are present in the same quadrant of the breast and separated by distances varying from 5 - 20 mm. This would exclude those cancers where the index lesion is surrounded in the immediate vicinity (/= 20% usually demands formal partial breast reconstruction.

Reply to comment 5 by Reviewer A
To be honest, we have not made an assessment of excisional breast tissue volume which will require formal partial breast reconstruction as 85% of our patients with MIBC are able to undergo successful BCS with only volume displacement techniques.
Fifteen percent of patients undergo mastectomy followed by reconstruction if desired. We do not have any patient who has undergone partial reconstruction in our patients with MIBC. Having said that, we agree that resection in excess of 20% of breast volume will result in significant deformity if no measures are undertaken to correct the defect.
However, because we adopt a technique where we rotate tissue to appose parenchymal walls in volume displacement, we translate that to a maximum of 70 degrees of rotation. Still, there are areas when this is more limited, like in the lower hemisphere of the breast where rotation may be limited to 45o to avoid distortion.
Reviewer A may have noticed that in Patient F, the parenchymal wall at the extremes may have to be rotated more than 90o for full apposition if the entire quadrant were excised to remove this multicentric tumour. However, applying lobar surgery with dual segment excision, there was an intervening tongue of tissue which remained attached to the periphery of the breast globe. Mobilisation of this tissue tongue with care so as not to disrupt the vasculature completely, and then drawing it down towards the nipple-areolar complex provided a buffer for rotation. So each of the extreme walls on either side of this intervening triangular-shaped tissue needed only to be rotated about 30o on each side to be apposed with this central pillar for complete closure of the defect. This same surgical approach was also applied for Patient C. (Editorial office: pictures are only available upon request from the editorial office).

As Reviewer A has correctly pointed out, this technique is not widely known despite it being published several years ago. Including these elaborate details might detract from the subject we wish to discuss, so we initially avoided broaching the percentage excisional breast volume which demands formal partial breast reconstruction. But we will include this now.
Changes in text (lines 314-317 of revised manuscript): The minority of patients who require resection in excess of 20% of total breast tissue volume may require therapeutic mammoplasty, volume replacement procedures or mastectomy with or without reconstruction.

Reviewer A's Comment 6 (paragraph 3):
The authors suggest that BCS was introduced in 1969 but this was the year Veronesi applied to WHO and indeed his proposal for a trial of BCS was rejected outright the first time. It was not until a consensus conference in 1990 that BCS was finally acknowledged in the United States as the preferred surgical treatment options (sic) for the majority of women with early stage breast cancer.

Reply to Reviewer A's Comment 6.
Thank you for pointing out that 1969 was the year that Veronesi applied to WHO and his proposed trial for de-escalation from mastectomy to BCS was rejected. It is not unusual that unknown surgical approaches or little known techniques are rejected, a circumstance which persists today.
We have amended the script, added a reference and trust that it would be acceptable. We also appreciate Reviewer A's comment that it was not until a consensus conference in 1990 (sic) that BCS was finally acknowledged in the United States as the preferred surgical treatment option for the majority of women with early stage breast cancer.
In a similar vein, at a consensus conference in 2015, (reference 21 in the manuscript), BCT was endorsed for MIBC as long as clear margins were achieved and whole breast irradiation was planned.
Change in text in the Introduction (lines 75-97 of revised manuscript):
For an extended period of time, the surgical treatment of breast cancer depended on the use of various forms of mastectomy, from the radical mastectomy, to modified radical and then total mastectomy. Although change was first suggested in the year 1969, it was not until some two decades later that breast conservation treatment (BCT) would be considered an appropriate alternative to mastectomy for the surgical treatment of breast cancer. (1,2)
Initially, the proposal to de-escalate surgical treatment for breast malignancies in 1969 was met with a great deal of scepticism and caution by several prominent clinicians and pathologists of the time,(3-5) who in turn described residual foci of carcinoma present after a simulated partial mastectomy, presence of multifocality and multicentricity in up to 63% of patients who were thought to have unifocal disease at presentation.
With the publication of early results of the Milan I and NSABP B-06 trial in the year 1985,(6,7) one of these dissenters had to concede that it was possible that radiotherapy may eradicate or impair indefinitely the progress or clinical viability of these occult foci of disease,(4) These early data supported surgical de-escalation and a consensus statement in the year 1991 established breast conservation treatment (BCT) as an appropriate alternative for

women with early stage breast cancer. (2) Twenty-year follow up of the NSABP B-06 study confirmed the ability of radiotherapy to effect local control similar for women who BCT as those who had total mastectomy.(8) More recently, there is compelling evidence to show that BCT results in superior survival and noninferior local control, (9-45) with several reviews supporting the findings of these studies(46- 51)
2.NIH Consensus Conference.
Treatment of early-stage breast cancer. JAMA 1991;265:391-5 Reviewer A, Paragraph 3
Reviewer A's Comment 7 (paragraph 3):
Moreover, they suggest that the MIAMI trial failed in part because many women with MIBC preferred BCS and did not want to be randomized with the possibility of then undergoing mastectomy. The latter remains the mainstay for treatment of MIBC…

Reply to Reviewer A's Comment 7
Please find attached excerpts from a qualitative study on the MIAMI trial. (reference 60 in the original manuscript/reference 100 in the amended manuscript) It is our understanding from the article and these excerpts was that surgeons were influenced by the St Gallen consensus statements in 2017, as well as in 2015 (references 21 & 22 before & references 61& 62 after amendments) where both Panels endorsed breast conservation for MFMCBC. Some surgeons found it difficult to inform patients that they should consider participating in the trial. However, we accept Reviewer A's comments and have edited our manuscript accordingly.
Change in text for Reviewer A's comment 7
(lines 391-397 of revised manuscript): However, the investigators for the MIAMI trial have reported dismal accrual to date as women eligible for the trial are resistant to randomisation.(100) Some patients actively decline mastectomy. This represents a significant shift in attitudes. When the concept of BCT for MIBC was first mooted a few decades ago, clinicians reported that it would be the exceptional patient who would qualify for conservative surgery.(60) However, women with MIBC now are more inclined to undergo BCT.(100)
Reviewer A's Comment 8 (paragraph 3): Moreover, there is a trend for maximal surgery these days with many women opting for bilateral mastectomy (and often immediate reconstruction) for small unilateral cancers that would otherwise be suitable for conventional BCS.

Reply to Reviewer A's Comment 8
We are aware that there is a trend for maximal surgery but this may be contrary to evidence in terms of survival benefit. Allow us to cite a recent article by Lim et al (JAMA Surg 2022;156:569-576): 'It can be argued that the decision for contralateral prophylactic mastectomy is not rational (emphasis ours) if it has arisen from an overestimation of the true level of risk.' In an era of de-escalation of chemotherapy and axillary surgery, performing mastectomy and contralateral mastectomy may be seen to be contradictory to these other concepts and contrary to available data with respect to survival outcomes and can be perceived as irrational.
Change in text for Reviewer A's Comment 7: none

Reviewer A, Paragraphs 4 & 5

Reviewer A's Comment 9: The authors have cited the work of Roland Holland but have not really described the key findings from his detailed anatomical dissections of mastectomy specimens – basically showing that tumour was present more than 2 cm from the index lesion in more than 40% of cases.

Reply to Reviewer A's Comment 9 (paragraph 4 & 5)

We thank Reviewer A for the informative paragraph on multifocal and multicentric tumours, despite having averred unfamiliarity with this term in paragraph 1. We trust that we have provided sufficient pictorial evidence in Patients A-E in this response (but not for the manuscript) to indicate that we are aware of Professor Holland's definition and have performed surgery for many patients who have tumour foci more than 2 cm apart or away from the index lesion. (Editorial office: pictures are only available upon request from the editorial office.)

If Reviewer A could provide us with the reference for his/her article, we will be happy to amend the manuscript as requested. At this juncture, we would like to state that the purpose of citing Professor Holland's work, and those of the other pathologists, was twofold: first, to demonstrate that this entity of MIBC was already known to exist prior to the era of BCT (which Reviewer A has kindly mentioned began in 1990) and second, to show that control can be effected with radiotherapy based on the results of the NSABP B-06 study.

Change in text: none at this point in time, pending reference from Reviewer A Reviewer A, paragraph 6

Reviewer A's comment 9 (paragraph 6):

I am surprised that there is no mention of the seminal paper by van Maaren and colleagues from the Netherlands who first presented retrospective (and confounded) evidence that overall survival may be superior for BCS compared with those undergoing mastectomy. … The authors refer to 'compelling evidence' and this is a key theme in the article.

Response to Reviewer A's comment 9:

We apologise that we have not included the seminal paper by van Maaren et al in the initial manuscript as our objective was to provide the most recent article we could locate with the highest number of patients. This was fulfilled in the paper by Dr De la Cruz et al. We also regret that we have to dispute the statement that van Maaren and colleagues were the researchers who 'first presented retrospective evidence that overall survival might be superior for BCS patients compared with those undergoing mastectomy.'

Please see an abbreviated (not exhaustive) list of the articles within our personal library concerning this subject, published before the 2016 article by van Maaren et al which included 37,207 patients.

1. Martin MA, Meyricke R, O'Neill T, Roberts S. Breast-conserving surgery versus mastectomy for survival from breast cancer: the Western Australian Experience. Ann Surg Oncol 2007;14: 157-164. (2787 women)

2. Bantema-Joppe EJ, de Munck L, Visser O, et al. Early-stage young breast cancer patients: impact of local treatment on survival. Int J Radiation Oncology Biol Phys 2011;81:e553-e559.

3. Hwang ES, Lichtensztajn DY, Gomez SL, Fowble B, Clarke CA. Survival after lumpectomy
and mastectomy for early stage invasive breast cancer: the effect of age and hormone receptor status. Cancer 2013;119:1402-1411 (112,154 patients)
3. Agarwal S, Pappas L, Neumayer L, et al. Effect of Breast Conservation Therapy vs Mastectomy on Disease-Specific Survival for Early-Stage Breast Cancer. JAMA Surg 2014; 149:267-74. (132,149 patients)
4. Hofvind S, Holen A, Aas T, Roman M, Sebuødegård S, Akslen LA. Women treated with breast conserving surgery do better than those with mastectomy independent of detection mode, prognostic and predictive tumour characteristics. Eur J Surg Oncol 2015; 41:1417-1422. (9527 patients)
5. Hartmann-Johnsen OJ, Karesen R, Schlichting E, Nygard JF. Survival is better after breast conserving therapy than mastectomy for early stage breast cancer: A registry-based followup study of Norwegian women primary operated between 1998-2008. Ann Surg Oncol 2015;22:3836-3845. (13,015 patients)
6. Saadatmand S, Bretveld R, Siesling S, Tilanus-Linthorst MMA. Influence of tumour stage at breast cancer detection on survival in modern times: population based study in 173 797 patients. BMJ 2015:351:h4901 doi:10.1136/bmj.h4901 (173,292 patients)
7. Morris A, Morris R, Wilson J, et al. Breast conserving therapy vs. mastectomy in early stage breast cancer: a meta-analysis of 10–year survival. Cancer J Sci Am 1997; 3: 6-12. (Please note that authors of this meta-analysis suggested the possibility of better survival with BCT in certain subgroups of patients but it is of interest that this information was published in the year 1997) This is a further list of articles reporting similar findings of superior survival following BCT when compared with mastectomy.
9. van Hezewijk M, Bastiaannet E, Putter H et al. Effect of local therapy on locoregional recurrence in postmenopausal women with breast cancer in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial. Radiotherapy and Oncology 2013; 108:190-196.
10. Keating NL, Landrum MB, Brooks JM et al. Outcomes following local therapy for earlystage breast cancer in non-trial populations. Breast Cancer Res Treat 2001; 125(3):803-813.
11. Brooks JM, Chrischilles EA, Landrum MB et al. Survival implications associated with variation in mastectomy rates for early-staged breast cancer. Int J Surg Oncol 2012; doi:10.1155/2012/127854
12. Plichta JK, Rai U, Tong R et al. Factors associated with recurrence rates and long-term survival in women diagnosed with breast cancer ages 40 and younger. Ann Surg Oncol 2016. Doi 10.1245/s10434-016-5404-z
13. Mogal HD, Clark C, Dodson R, Fino NF, Howard-McNatt. Outcomes after mastectomy and lumpectomy in elderly patients with early-stage breast cancer. Ann Surg Oncol 2017; 24:100-107.
14. Nandakumar A, Rath GK, Kataki AC et al. Decreased survival with mastectomy vis-à-vis breast-conserving surgery in stage II and III breast cancers: a comparative treatment effectiveness study. J Glob Oncol 2017;3(4)
15. Hartmann-Johnsen OJ, Karesen R, Schlichting E, Nygard JF. Better survival after bareast-conserving therapy compared to mastectomy when axillary node status is positive in

early-stage breast cancer: a registry-based follow up study of 6387 Norwegian women participating in screening, primarily operated between 1998 and 2009. World J Surg Oncol 2017;15:118
16. Christiansen P, Cartensen SL, Edlertsen B, et al. Breast conserving surgery versus mastectomy: overall and relative survival – a population based study by the Danish Breast Cancer Coooperative Group (DBCG) Acta Oncol 2018;57:19-25.
17. Lagendijk M, van Maaren MC, Saadatmand S, et al. Breast conserving therapy and mastectomy revisited: breast cancer-specific survival and the influence of prognostic factors of 129,692 patients. Int J Cancer 2018;142:165-175.
18. Fisher S, Gao H, Yasui Y et al. Survival in stage I-III breast cancer patients by surgical treatment in a publicly funded health care system Ann Oncol 2015;1161-1169.
19. Kim K, Park HJ, Shin KH et al. Breast conservation therapy versus mastectomy in patients with T2N1 triple-negative breast cancer: pooled analysis of KROG 14-18 and 14-23. Cancer Res Treat. 2018; 50:1316-1323.
20. Fakhreddine MH, Haque W, Ahmed A et al. Prognostic factors, treatment and outcomes in early stage, invasive papillary breast cancer: SEER investigation of less aggressive treatment in a favourable histology. Am J Clin Oncol 2018; 41: 532-537.
21. de Boniface J, Frisell J, Bergkvist L, Andersson Y. Breast-conserving surgery followed by whole-breast irradiation offers survival benefits over mastectomy without irradiation. Br J Surg 2018;105:1607-1614
22. Wang J, Wang S, Tang Y et al. Comparison of treatment outcomes with breastconserving surgery plus radiotherapy versus mastectomy for patients with stage I breast cancer: a propensity score-matched analysis. Clin Br Cancer 2018;18:e975-84
23. Arlow RL, Paddock LE, Niu X, et al. Breast-conservation therapy after neoadjuvant chemotherapy does not compromise 10-year breast cancer-specific mortality. Am J Clin Oncol 2018;41:1246-1251.
24. Corradini S, Reitz D, Pazos M et al. Mastectomy of breast-conserving therapy for early breast cancer in real-life clinical practice: outcome comparison of 7565 cases. Cancers 1029;11:160
25. Lazow S, Riba L, Alapati A, James TA. Comparison of breast-conserving therapy vs mastectomy in women under age 40: national trends and potential survival implications. Breast J 2019;00:1-7. (We would like to highlight that this study explores survival with bilateral mastectomy as well, which was mentioned in paragraph 3 of Reviewer 1's comments)
26. Almahariq MF, Quinn TJ, Siddiqui Z, et al. Breast conserving therapy is associated with improved overall survival compared to mastectomy in early-stage, lymph node-negative breast cancer. Radiotherapy and Oncology 2019. Doi.org/10.1016/j.radond.2019.09.018
27. Wrubel E, Natwick R, Wright GP. Breast-conserving therapy is associated with improved survival compared with mastectomy for early-stage breast cancer: a propensity score matched comparison using the national cancer database. Ann Surg Oncol 2020. doi.org/10.1245/s10434-020-08829-4.
28. Wen S, Manuel L, Doolan M et al. Effect of clinical and treatment factors on survival outcomes of triple negative breast cancer patients. Breast Cancer: Targets and Therapy 2020:12:27-35.

29. Akbari ME, Khayamzadeh M, Mirzaei HR et al. Saving the breast saves the lives of breast cancer patients. Int J Surg Oncol 2020:8709231.
30. Chu QD, Hsieh MC, Lyon JM, Wu XC. 10-year survival after breast-conserving surgery compared with mastectomy in Louisiana women with early-stage breast cancer: a population-based study. J Am Coll Surg 2021;232:706-621.
31. Wan QT, Su LM, Ouyang T et al. Comparison of survival after breast-conserving therapy vs mastectomy among patients with or without the BRCA1/2 variant in a large series of unselected Chinese patients with breast cancer. JAMA Netw Open 2021;4:e216259.
32. Chu QD, Hsieh MC, Yi Y et al. Outcomes of breast-conserving surgery plus radiation vs mastectomy for all subtypes of early-stage breast cancer: analysis of more than 200,000 women. J Am Coll Surg 2022;234:450-464.
33. Saifi O, Chahrour MA, Li Z et al. Is breast conservation superior to mastectomy in early stage triple negative breast cancer? Breast 2022;62:144-151.
34. Li P, Xiu B, Zhang L, et al. The prognoses of young women with breast cancer (<35 years) with different surgical options: a propensity score matching retrospective cohort study. Frontiers Oncol 2022;12:795023. Doi:10.3389/fonc.2022.795023 In addition to the above studies, there are also opinion pieces regarding the use of BCT and mastectomy based on the current evidence.
35. Johns N, Dixon JM. Should patients with early breast cancer still be offered the option of breast conserving surgery or mastectomy? EJSO 2016;42:1636-1641. 36. McCormick B. The mastectomy myth. Lancet Oncol 2016;
37. Gentilini O, Cardoso MJ, Poortman P. Less is more. Breast conservation might be even better than mastectomy in early breast cancer patients. Breast 2017;35:32-33
38. Fancellu A. The need to diminish mastectomy rates in patients with breast cancer eligible for breast conservation. Updates in Surgery 2019;71:597-598.
39. Hartmann-Johnsen OJ. Breast-conserving therapy is better than mastectomy based on registry data from Norway. PhD Thesis, University of Oslo.
40. Murphy J, Gandhi A. Does mastectomy reduce overall survival in early stage breast cancer? Clin Oncol 2021;33:440-447.

Amongst these authors, may we cite a few notable quotes. Fisher et al suggests ‘greater efforts toward educating and encouraging patients to receive BCS plus radiotherapy rather than mastectomy when it is medically feasible and appropriate’.
Johns and Dixon, in 2016, concluded that ‘it no longer seems logical to offer all patients with early breast cancer, who are not gene carriers the option of BCT or mastectomy. Such patients should be advised that BCT is their optimal treatment.’ Akbari et al categorically state in their article that ‘Saving the breast saves the lives of breast cancer patients.’ We are aware that the list of articles is not exhaustive and there are likely more articles demonstrating similar outcomes and viewpoints.
However, we hope we have shown sufficient cause to Reviewer A why we use the term ‘compelling evidence’ when we prefer the use of BCT over mastectomy.
Change in text (lines 442-573 of revised manuscript): we have included all the above references, including the paper by van Maaren to address Reviewer A’s comments. Thank you

Paragraph 7 Reviewer A's comment 10 (paragraph 7):
I notice the PubMed search was for articles published from 1970 – but at this time few patients were having BCS and certainly nor for MIBC. The search criteria are quite broad and the authors fail to mention how many articles appeared after the first search (which was then reviewed for duplication) (please note that about 20% of phyllodes tumours are malignant).
Reply to Reviewer A's Comment 10
We are aware that very few patients, perhaps none, underwent BCT in the 1970s. However, Reviewer A will recall with us that the pathologist Peter Rosen and colleagues discussed the presence of 'residual carcinoma after simulated partial mastectomy' in the year 1975 while Michael Lagios introduced 'multicentricity in breast carcinoma' in the year 1977.
Our purpose was to discover if there was any other significant information about MIBC during that period. As it stands, we don't know of any. As mentioned earlier in paragraph 1 of this response, we did a repeat Medline search on PubMed on 6 Dec 2022 with the terms listed. This yielded a total of 167 citations. The term 'sick lobe hypothesis' yielded 15 articles and 'field cancerization AND genetic changes AND breast margins' revealed 10 articles. These specific search terms provided a total of 192 articles, instead of the 226 originally identified with our broader search terms. The necessary amendments have been made and we thank Reviewer A for highlighting the matter.
In Diagram 1 of the initially submitted manuscript, we had indicated that we had excluded 'non-carcinomatous lesions'. It is our understanding that phyllodes tumours is not a carcinoma and will be happy to stand corrected by Reviewer A if we are mistaken on this. In any case, we have included patient H in our response. This patient had two lesions, 38.9 mm & 41.6 mm at their respective largest dimensions. As you can see, the principles of resection are no different. In her case, we were able to achieve clear margins for borderline phyllodes tumours, and she has remained free of local recurrence for more than 10 years. We have only encountered malignant phyllodes in two patients and since they presented very late, mastectomy was performed. However, both unfortunately succumbed to their disease within months of their presentation from uncontrolled disease progression.
Change in text for Reviewer A's Comment 10 (lines 105-109 of revised manuscript):
A PubMed search was performed for articles published from 1970 to November 2022 in the English language with the terms: 'multifocal multicentric breast cancer AND breast conservation treatment' (101 articles), 'multiple ipsilateral breast cancer AND breast conservation treatment' (66 articles), 'sick lobe hypothesis'(15 articles), and 'field cancerisation AND genetic changes AND breast margins'(10 articles).

Reviewer A's comment 11 (paragraph 7):
I would challenge the claim that early randomized trials of BCS such as NSABP B-06 showed that local recurrence rates were lower for patients receiving lumpectomy and radiotherapy than mastectomy…
Reply to Reviewer A's comment 11: Please find attached to following excerpts.
First, from Professor Bernard Fisher's article in NEJM, page 1236. (Full reference 8 in manuscript): Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomised trial comparing mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment

of invasive breast cancer. N Engl J Med 2002; 347:1233-41.) We were referring specifically to this article, but for good measure, we have included other articles as well.
Second, from van der Heiden-van der Loo (Ann Surg Oncol 2015;22:2522-8. Third, from an earlier prospective study, the TEAM trial (reference 9 in this response): These three large studies suggest that breast conserving surgery followed by radiotherapy confers numerically lower recurrence rates, although they may not be statistically significant in every circumstance.
Change in text for Reviewer A's comment 11 (line 128 in revised manuscript):
Yet, it was found that there was no difference in overall survival and in the NSABP B-06 study, data suggested that local recurrence rates were numerically lower for women who underwent lumpectomy with radiotherapy than for those who underwent mastectomy.(8)

Reviewer A Paragraph 8 Reviewer A's comment 12 (paragraph 8):
I agree that that rates of IBTR are similar for MIBC and for unifocal lesions. However, the authors refer to recent articles that predominantly relate to the period 1990 -2009. … There should be much clearer information as to whether MIBC are associated or not with higher rates of locoregional or distant disease recurrence.

Reply to Reviewer A's comment 12:
We thank Reviewer A for stating that published data indicates that rates of IBTR are similar for MIBC as for unifocal lesions. Although this is slightly different from our understanding, we would be happy to revisit this and change our text according to Reviewer A's article. In line 156-158 of our original manuscript, (lines 157-159 of the revised manuscript) we stated that 'The presence of multiple ipsilateral foci of mammary malignancy is a poor prognostic indicator; however, higher locoregional and distant relapse was observed independently from the type of surgery performed.' (references 23-25 of our original manuscript & references 63-65 of our revised manuscript) With respect to the publication dates of the cited articles, in the original submission, we had included 6 articles from the period to which Reviewer A refers, 1990 to 2009 (references 15- 20), but we wish to highlight that we have also included 14 articles which have important references to multifocal multicentric breast cancers published from the year 2010 to the year 2022. (references 12,13,14,21,22,23,24,25,26,27,40, 52,59,60) (The corresponding references in the revised manuscript are 52-67,80,92,99,100 in the revised manuscript.) This excludes the authors' 4 own published articles on multifocal multicentric breast cancers between 2015-2017 in the reference list. In total there are 18 articles on MIBC from the years 2010 to 2022. We hope therefore to be absolved of referring to 'recent articles that predominantly relate to the period 1990 – 2009.' Our purpose in including the earlier articles was to demonstrate the shift in treatment philosophy and outcomes over the years.
Change in text for Reviewer A's comment 12: none so far, pending articles from Reviewer A

Reviewer A, paragraph 8 Reviewer A's comment 13 (paragraph 8):
there is no mention of margin width in the context of tumour excision – the authors refer to clear margins – are these 'no tumour on ink' or wider margins?

Reply to Reviewer A's comment 13

We will admit that there was a conflict in our minds regarding clear margins. Currently, we subscribe to the consensus statement issued at the St Gallen International Breast Cancer Conference 2015 (reference 21 in our original manuscript/ reference 61 in the revised manuscript) where 'the minimal acceptable margin was no ink on invasive tumour or DCIS' and 'A clear majority of the Panel agreed that multifocal and multicentric tumours could be treated with breast conservation, provided the above margin was obtained and whole breast irradiation was planned.'

However, since we were suggesting that a different standard may be applied, in that we were proposing the use of the presence of molecular changes in histologically normal appearing tissue as markers for clear margins, we may end up contradicting ourselves. This was the reason why we omitted defining clear margins. However, since both Reviewers A & B have highlighted the issue of margins, we have addressed it and hope that it will be acceptable.

Change in text for Reviewer A's comment 13 (under heading Field Cancerisation and Surgical Resection Volumes, lines 263-273 in revised manuscript):

Excising the 'sick segment' poses the dilemma of what constitutes a negative margin. The current consensus for a clear margin is 'no ink on tumour' for invasive disease and some experts advocate 2 mm margins for ductal carcinoma in situ (DCIS). (61,62) The concept of the sick segment with identification of molecular changes at the margins of histologically normal tissue introduces another dimension which may appear contradictory. A change in definition of a clear margin is not propounded at this point in time.

However, the authors suggest that more research is required in this area, and there may be a role for de-escalating radiotherapy if marginal tissue do not demonstrate molecular changes which confer predilection for carcinogenesis. This potentially enables individualised treatment, just as genomic signatures inform systemic therapy.

Reviewer A's Comment 14 (paragraph 10):

There is minimal reference in the literature to the 'sick lobe hypothesis' but the authors focus on this quite heavily in the article and indeed this is a central theme. They fail to appreciate that the ductal-lobular system of the breast has a complex pattern of arborization and different ductal systems are intertwined in a 3-dimensional manner.

Reply to Reviewer A's comment 14

We agree with Reviewer A that there is very little information on the subject of the sick lobe hypothesis in medical literature. A Medline search on PubMed on 6 Dec 2022 for 'sick lobe hypothesis' yielded 15 citations.

Comparatively, 'breast conservation treatment' returned 12,316 results on the same day.

Here we see the divergent interest even though fundamentally, these issues are related. The relatively close time lines for articles for the first consensus statement endorsing BCT (1991) and early discussion of the sick lobe hypothesis (1996) are noteworthy.

BCT was accepted as appropriate treatment in the 1990s, while Moffat and Going first discussed the anatomy and pathology of the duct system in the human breast in the year

1996. Despite being relatively close chronologically in their first appearance in medical literature, these two concepts were divorced from each other for almost 3 decades even though the core principles are interrelated.
As authors, we are bringing these 2 concepts together to offer better surgical planning and hopefully treatment outcomes for patients. In our manuscript, there are 17 references to breast duct anatomy, embryology and breast tissue development, carcinogenesis and the sick lobe hypothesis. The details alluded to in these 17 references necessarily need to be combined to develop a coherent concept of the sick lobe hypothesis since there are very few 'ready-made' references in the literature concerning the sick lobe. We are acutely aware of the fact that the ductal lobular system of the breast has a complex three-dimensional pattern of arborisation and intertwining.
Moffat and Going (reference 74 in the revised manuscript) have published on this. However, Sir Astley Cooper's work demonstrates that the ducto-lobular system follows a pyramidal distribution, and as Edgerton et al has calculated, this approximates an ellipse in a 'living breast'. We are aware that it is not possible to eliminate the entire distribution of the sick lobe in all cases, but we can plan resection to remove the main body of the affected ductolobular segment as much as possible. This carries a two-fold purpose.
The first being to remove as much of the diseased lobe as possible, and the second, following the natural distribution of the sick lobe as closely as surgical resection will allow provides a defect pattern that can be closed without the need for tissue replacement.
Please see pictures relating to the surgical treatment for Patient G. In her case, the entire sick lobe 'declared' itself on imaging preoperatively. In such circumstances, we can confidently plan the surgical approach with bracketing wires, and using the principle of the sick lobe, resect a tissue ellipse around the bracketing wires, mobilise the remaining parenchymal walls, rotate them and appose with sutures. (Editorial office: pictures are only available upon request from the editorial office).
This patient is disease free 18 years after treatment, with her natural breast and without tissue replacement. Lass et al (reference 99 of revised manuscript) have reported the use of augmented reality to superimpose the estimated resection volume onto an avatar of the patient. This computer generated image was used to guide surgery in a real patient. In the same vein, this can be performed for women with MIBC, perhaps resembling the use of augmented reality in neurosurgery.
Change in text for Reviewer A's comment 14: none

Reviewer A, Paragraph 10 Reviewer A's
comment 15 (paragraph 10): I am uncertain how the authors propose to apply this hypothesis of the sick lobe syndrome to surgical resection of multifocal/multicentric cancers.

Reply to Reviewer A's comment 15:
Kindly refer to photographs of patients A-G (Editorial office: pictures are only available upon request from the editorial office).
Change in text for Reviewer A's comment 15: none

Reviewer A's comment 16: How can the extent of any molecular or genetic alterations within an individual lobe be delineated prior to surgery ad be confidently resected without necessitating removal of excessive amount of breast tissue.

Reply to Reviewer A's comment 16
We thank Reviewer A for asking how genetic alterations can be highlighted prior to surgery for we have inserted this in the manuscript. We apologise if we are repetitive. We have suggested how this may be done in our response to Reviewer A's comment 2 but we repeat it here for easy reference.
Changes in the text (under future directions for BCT in MIBC, lines 374-384 in our revised manuscript):
Medicine has moved into the era of immunotherapy and functional imaging, each of which has been used for more than a decade. Combining the concepts from these available technologies, we envisage that it would be possible to develop a physiological substrate which might tag the genetic change(s) identified on preoperative core biopsy. Using this, a functional imaging modality similar to positron emission tomography (PET scan) might be used to locate the sites at which the substrate has attached to within the breast. Using augmented reality, just as Laas et al have described, an estimated resection volume can be superimposed onto an avatar of the patient and used as a guide for surgery. Although much research is required before this can become a reality, the authors believe that this development is possible in the not too far future.

Reviewer A's Comment 17:
Removal of a single elliptical segment is rather like the old-fashioned quadrantectomy but this has been superceded by modern methods of oncoplastic breast surgery that can resect tumour with wide margins, low rates of IBTR and excellent cosmetic outcomes…

Reply to Reviewer A's Comment 17: Thank you for your comment. We are reminded of a story of two different countries competing to build the first space station. One country spent a significant amount of resources to develop a hi-technology pen which would allow ink-flow in a gravity-free situation for their astronauts to use in space. The other country got its astronauts to use old-fashioned pencils.
Change in text for Reviewer A's Comment 17: none; Please see attached operative photographs intended for reviewers.

Reviewer A's comment 18 (paragraph 11):…there is a disparity between rates of response to NACT and adoption of BCS – rates of BCS after NACT are much lower and may actually reflect a desire of patients to undergo mastectomy rather than BCS after NACT.
Reply to Reviewer A's comment 18: Pardon us for being repetitive here again but we attach an excerpt from the article by Dr Fisher et al. (Fisher S, Gao H, Yasui Y et al. Ann Oncol 2015;1161-1169).
Change in text for Reviewer A's Comment 17: none
Reviewer A's comment 19:
Which patients Should get MRI imaging?

Reply to Reviewer A's comment 19

The use of MRI is controversial. In her article published in J Am Coll Surg 2020;230:331-339 Dr Lisa Newman (reference 53 of original manuscript/reference 93 of revised manuscript) stated that the American Society of Breast Surgeons advises against routine use of preoperative MRI in breast cancer patients because it carries the risks of delaying definitive operation and increasing the likelihood that a patient will be triaged toward mastectomy.
Please see Patient J who underwent breast MRI for rapid progress of disease over 6 months and was found to have 3 other subcentimetre suspicious lesions.
To expedite treatment, she elected for localisation excision biopsy of the other lesions at the time of definitive surgery for her cancer. Lesions in the other 2 quadrants of the breast were benign, illustrating the possibility of false positive results on MRI.
The authors wonder if she had undergone treatment elsewhere whether a mastectomy would have been performed instead. According to the multiple articles listed earlier in this response, mastectomy is associated with poorer survival.
We wonder if this also has medicolegal implications if women eligible for BCT were to undergo mastectomy. At the same time, we are aware that there are proponents of MRI especially in the setting of NACT. Our practice is to use MRI very sparingly, only when there is reason to suspect that conventional imaging may not depict the extent of disease adequately.
We routinely place marker clips within each tumour foci and localise all lesions detected by conventional imaging only.
Please see patient D. Occasionally, our patients may come from another centre with an MRI already performed. In those cases, operative planning will be undertaken with MRI findings in mind. (Editorial office: pictures are only available upon request from the editorial office).

Change in text for Reviewer A's comment 19 (lines 330-332 in revised manuscript):

The authors apply MRI only if there is strong clinical suspicion that conventional imaging with mammogram and ultrasound has not adequately delineated the extent of disease.

Reviewer B

The authors are immensely grateful to Reviewer B for constructive comments.

Reviewer B, comment 1:

Radical mastectomy was not the mainstay of surgical treatment until 1969. Modified radical mastectomy and then total mastectomy were utilized until BCT trials supported deescalation.

Reply to Reviewer B, comment 1.

Thank you for your comment. We have amended the manuscript and hope it meets with your approval.

Change in text (lines 75-97 in revised manuscript):

For an extended period of time, the surgical treatment of breast cancer depended on the use of various forms of mastectomy, from the radical mastectomy, to modified radical and then total mastectomy. Although change was first suggested in the year 1969, it was not until some two decades later that breast conservation treatment (BCT) would be considered an

appropriate alternative to mastectomy for the surgical treatment of breast cancer. (1,2) Initially, the proposal to de-escalate surgical treatment for breast malignancies in 1969 was met with a great deal of scepticism and caution by several prominent clinicians and pathologists of the time,(3-5) who in turn described residual foci of carcinoma present after a simulated partial mastectomy, presence of multifocality and multicentricity in up to 63% of patients who were thought to have unifocal disease at presentation. With the publication of early results of the Milan I and NSABP B-06 trial in the year 1985,(6,7) one of these dissenters had to concede that it was possible that radiotherapy may eradicate or impair indefinitely the progress or clinical viability of these occult foci of disease,(4) These early data supported surgical de-escalation and a consensus statement in the year 1991 established breast conservation treatment (BCT) as an appropriate alternative for women with early stage breast cancer. (2) Twenty-year follow up of the NSABP B-06 study confirmed the ability of radiotherapy to effect local control similar for women who BCT as those who had total mastectomy.(8) More recently, there is compelling evidence to show that BCT results in superior survival and non-inferior local control, (9-45) with several reviews supporting the findings of these studies(46-51)

Reviewer B comment 2:

Adequate margins for invasive breast cancer are no tumour on ink and 2 mm for DCIS. There is no advantage to wiser margins for lower risk of recurrence. The theory of sic lobe suggests those with 'molecularly primed tissue' are at higher risk for recurrence if this wider margin is not resection. If this theory is true, then radiation appears to adequately control the sick lobe. Perhaps this is the value of a boost to the lumpectomy cavity. Please discuss.

Reply to Reviewer B, comment 2

Thank you for your comments. As we mentioned in one of our replies to the other reviewer, we were concerned that in discussing margin status, we might introduce complex issues that do not have an abundance of evidence, or we may contradict ourselves. We agree with your definition of an adequate margin. Perhaps an absence of molecular changes in histologically normal tissue might indicate a decreased need for radiotherapy and this might assist in treatment selection, just as genomic studies inform systemic therapy. Of course, this would require an immense amount of research moving forward and we can only speculate the possibilities. Accordingly, we have added a paragraph in our manuscript.

Change in text (under the heading Field cancerisation and Surgical resection volumes, lines 263-273 in revised manuscript):

Excising the 'sick segment' poses the dilemma of what constitutes a negative margin. The current consensus for a clear margin is 'no ink on tumour' for invasive disease and some experts advocate 2 mm margins for ductal carcinoma in situ (DCIS). (61,62) The concept of the sick segment with identification of molecular changes at the margins of histologically normal tissue introduces another dimension which may appear contradictory. A change in definition of a clear margin is not propounded at this point in time. However, the authors suggest that more research is required in this area, and there may be a role for de-escalating radiotherapy if marginal tissue do not demonstrate molecular changes which confer predilection for carcinogenesis. This enables individualised treatment, just as genomic signatures inform systemic therapy.

Reviewer B, Comment 3:

I would propose there are not many surgeons doing ‘lobar surgery’ at the time of lumpectomy and many are leaving this ‘molecularly primed tissue’ behind without a significant recurrence risk.

Reply to Reviewer B, Comment 3

We agree with this statement. However, as we explained in the previous paragraph, there may be a role in future, after sufficient evidence, that the absence of genetically altered tissue at the specimen margins may inform de-escalation of radiotherapy.

The other, more essential role of the sick segment is the application of the concept for multifocal and multicentric disease. Understanding the geometry of the sick segment allows tissue resection design planning. As mentioned in our response to Reviewer A, we envisage the possibility of using functional imaging to detect areas with carcinogenic potential, combine it with conventional imaging, use artificial intelligence and augmented reality to estimate resection volume.

The computer generated images can be superimposed on an avatar, or on the patient herself, and used to direct surgical dissection, much like how it is done in neurosurgery. Once again, thank you for your helpful comments.

Change in text: none

We wish to thank both Reviewers for helping us improve our manuscript.