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The reoperation lottery

EMMA MASON

The odds that a woman will be told she needs a reoperation after conservative breast surgery vary between treatment centres, prompting calls for international guidelines – and greater oversight of surgeons.

For many women with early breast cancer, hearing that they can safely be treated with breast-conserving therapy comes as a big relief. What they don't want to hear is that they will have to undergo a second surgery, because the 'margin' of cancer-free tissue cut out from around the tumour is deemed unsafe. Getting it right first time may not always be possible, but growing evidence of big differences in reoperation rates between different centres is raising questions about how many women may be undergoing unnecessary reoperations, and why. Attention is focusing on the need for consensus guidelines on what constitutes a 'safe' margin and how it should be measured.

Ensuring sufficient tissue is excised to minimise the risk of the tumour returning is important, because a local recurrence not only causes the woman extra distress, but is also associated with reduced survival. But reoperating where the margins are judged to have been insufficient also comes at a cost – physical, emotional and financial – so it is important to ensure that women are only referred back for further surgery when there is good evidence to show it is needed.

The need for a greater consensus and more uniform practice regarding when women should be sent back for reoperation was highlighted last July in an article by Ranjeet Jeevan and colleagues in the *British Medical Journal* (vol 345, e4505). The study reported that, on average, around 20% of women who had breast conserving surgery in England had a reoperation, but that the rate of reoperation varied widely from centre to centre. "Some English NHS trusts had adjusted reoperation rates below 10%, whereas for others it was above 30%."

Examining the potential reasons behind such variations, the authors argue that it cannot be explained by patient preference alone. "The variation is sufficiently large to suggest that it reflects differences in clinical practice at various points during the therapeutic pathway, as well as patients' preferences. Practice related causes of variation could include differences in selection protocols for breast conserving surgery, poor surgical technique, and differences in how resection margins are assessed…" They suggest that the "lack of consensus on what constitutes an adequate excision margin" is probably an important factor, and they note that this is not just a UK problem; similar studies have shown reoperation rates of 29% in The Netherlands, 23% in the US, and 21.5% in Germany – again with significant variations in the rates reported by different hospitals.

Bigger 'is not better'

The publication of the *BMJ* article coincided with a 'sounding board' editorial in the *New England Journal of Medicine*, by Monica Morrow, chief of the breast surgery service at the Memorial Sloan-Kettering Cancer Center, New York, that focused on unnecessary reoperations. Under the title "Surgical margins in lumpectomy for breast cancer – bigger is not better" (*NEJM* 2012, 367:79–82), Morrow argues that in many centres women are being reoperated to achieve margins of between 2 and 5 mm, or even more, which cannot be justified by the evidence.

"…20 to 30% of women who undergo breast-conserving surgery require additional breast surgery (re-excision) after the initial lumpectomy, with its associated illness and cost. Approximately half of these procedures are performed in women with negative margins [i.e. no cancer cells at the edge] to obtain a wider clear margin in the belief that a wider margin will further decrease the risk of local recurrence," she writes.

Available data, she argues, do not support the view that wider cancer-free surgical margins reduce the risk of the cancer returning, while there is plenty of evidence that when the cancer is removed with a narrow margin, adjuvant radio- and chemotherapy is effective in controlling local recurrence after surgery.

Among the evidence called on to back up this argument she cites a meta-analysis of 21 studies that showed no statistically significant difference in local recurrence in early-stage invasive breast cancer between margins of 1, 2 or 5 mm after adjusting for the use of radiation and hormone therapy.

The big predictors of recurrence, she argues, have been shown to be tumour biology and the adequacy of systemic therapy. "These data necessitate a shift in thinking regarding the relationship between the width of microscopic margins and the risk of local recurrence." She suggests that such a rethink could see a major reduction in reoperations for women with clear margins, resulting in a decrease in costs and better cosmetic outcomes.

Mike Dixon, professor of breast surgery and consultant surgeon at the Western General Hospital in Edinburgh, was

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one of the co-authors of the meta-analysis that demonstrated no benefit from margins wider than 1 mm in early-stage invasive breast cancer. He argues that the difference between 1 mm and 5 mm is very significant in terms of the damage done to the way the breast looks.

"You have to leave the breast looking normal," says Dixon. "It's very easy to get all the disease out by taking a wedge out of the breast, but you're going to leave a big dent, a poor cosmetic result, and that is no advantage to the patient. That's why people like me are so obsessed with getting clear but not wide margins, because this allows me to achieve adequate long-term local control, but more importantly it allows the breast to look normal and gives the patient the advantage of a good cosmetic outcome.

"We know that if you do breast conserving surgery and it looks ugly, then the patient is not satisfied, and all the psychological advantages of breast conserving surgery in terms of ability to wear normal clothes, looking good in the mirror, the patient being more confident with good self-esteem and good body image disappear. The benefits of breast conservation are only there if you maintain a good breast shape and a volume that matches your other breast. What we want to do is get the disease out with a little bit, but not too much, normal tissue, and then good radiotherapy and good drug therapy to take care of any remaining disease, and then the patient will have an adequate long-term control and a satisfactory looking breast."

Dixon, whose own centre has been using a 1 mm margin for invasive early breast cancers for more than 10 years, with a five-year local recurrence rate of 1.7%, would like to see a consensus "around a 1 or 2 mm margin", to reduce the number of women who have unnecessary reoperations. "At present, some patients with clear margins of 1 or 2 mm are not only getting a second operation, some are getting a mastectomy!"

Towards a consensus

If the evidence is as strong as Morrow and Dixon claim, the question is why such a consensus is not already in place. One answer may be that leading breast cancer specialists do share a broad consensus – but this is not yet reflected in standard practice. In 2008 a group of opinion leaders from the US and Europe met in Frankfurt to formulate consensus recommendations on the locoregional treatment of primary breast cancer. Convened on the initiative of Manfred Kaufmann, head of gynaecology and obstetrics at the JW Goethe University hospital, Frankfurt, the group included leading oncologic surgeons, radiation oncologists, pathologists, radiologists, plastic surgeons, medical and gynaecologic oncologists, and epidemiologists. Their recommendations, which were published in 2010 (*Cancer* 116:1184–91), were that to minimise the risk of recurrence:

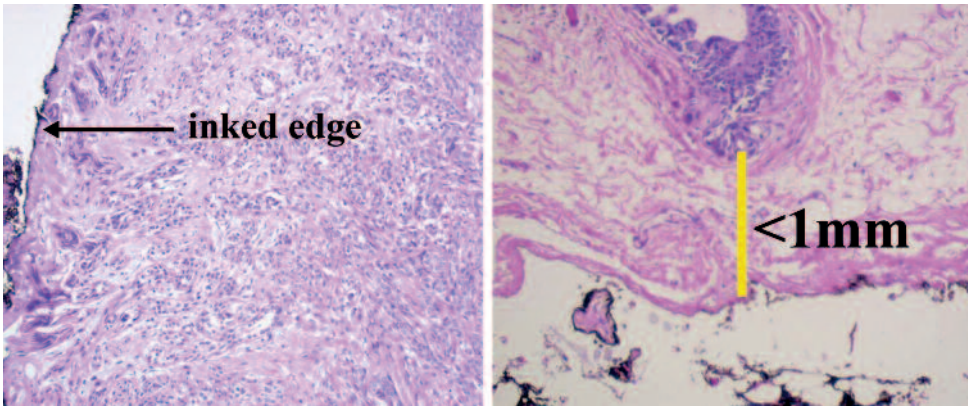
- In general, in cases of positive margins – where cancer cells are visible under the microscope at the surface of the excised tissue – reoperation is required.
- In the case of negative margins – i.e. no cancer cells at the surface of the excised tissue – reoperation is not required in cases of invasive breast cancer, even where the distance between the surface and the closest tumour cells is less than 1 mm.
- In cases of ductal carcinoma *in situ* (DCIS), however, a minimum clear margin of 2 mm is recommended, particularly with low- and intermediate-grade lesions, because DCIS may grow discontinuously within the ducts.
- Anterior and posterior margins of less than 2 mm are not of concern if there is no residual breast tissue.
- All suspicious microcalcifications associated with the DCIS should be removed surgically.
- Lobular carcinoma *in situ* at the margin is not considered an indication for further surgery.

While the wide variations recorded in reoperation rates indicate that many centres are not following these recommendations in practice, neither the recommendations, nor the evidence they have been drawn from, are being fundamentally challenged. The problem, therefore, may lie in how to move from consensus recommendations to effective national guidelines that ensure all women are treated according to the same standards wherever they are.

How good is your pathology?

But there may be other factors that also explain the variability in reoperation rates. Giuseppe Viale, head of pathology at the European Institute of Oncology in Milan, who participated in the expert panel that drew up the recommendations, says the quality of specimen processing and the assessment of surgical margins can vary greatly between different pathology departments. This means

MEASURING THE MARGINS



Following surgery, the excised tissue is 'inked' so that, when thin slices are cut and examined under a microscope, the edge of the tissue is clearly delineated. Pathologists need clear guidelines to ensure their examination of margins is sufficiently thorough and they understand the significance and implications of what they find.

that even if uniform criteria for reoperation are applied, different centres may reach different decisions on a given specimen, because of variations in the way the margins are measured and evaluated.

The standard procedure is to apply ink to the surfaces of the excised tissue. Thin slices are then cut, which are placed under a microscope, where the pathologist can see how close cancer cells come to the inked edge of the excised tissue. But tumour tissue can be tricky to handle, with a tendency to lose its shape and fall apart when sliced thin. And it can be difficult to get a reliable 'all round' view, because samples are taken 'at random', and each slice represents only one cross-section in one particular plane.

Variations in terminology can also give rise to confusion. As Dixon explains, some surgeons define a 'cancer-free margin' as one where there was no ink on a cancer cell. So even if there was a microscopically small distance between a cancer cell and the ink, it would still be a cancer-free margin. "However, most other people use distance. Some studies have used 2 mm, so they would say that if there were cancer cells within 1–2 mm of the edge of the specimen that would be a 'positive margin', and if the distance was more than 2 mm it would be 'negative margin'. But within the 1–2 mm margin distance, a large percentage of those patients would have 'cancer-free margins', because there isn't cancer at the edge."

Pathologists also need to understand the significance of what they are seeing; for instance, if lobular carcinoma *in situ* (atypical cells that are not invasive and are confined to the lobules in the breast) is found at the margins of the tissue, or if margins have only minimal tumour involvement, then further surgery is not necessarily required, says Viale. "This is especially the case for tumour types that have a favourable prognosis, such as luminal tumours and grade 1 tumours. The risk of local recurrence in these cases may be greatly reduced by radiotherapy and proper systemic treatments."

Viale believes there is a need for more guidelines and quality control to ensure patients and doctors can have confidence in the pathology assessments. "Practice in pathology departments should be standardised to allow at least a 'minimal' assessment of the margins; i.e. close examination of the margins nearest to the tumour, and the margin behind the nipple in the case of nipple-sparing mastectomy. Each department may then examine further the margins, but at least those I have mentioned should be evaluated in a standard fashion." Again it comes down to effective guidelines, he says. "National and international guideline recommendations should be strictly followed. Where national guidelines have not been issued, these should be prepared in accordance with the international recommendations."

Getting it right first time

While a more uniform approach to what constitutes an adequate margin, and how that should be measured, should decrease the number of women who are unnecessarily referred for

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reoperation, there will still be cases where reoperations are required, because insufficient tissue was removed first time round.

In the *BMJ* study, Jeevan and colleagues noted that reoperation rates were particularly high in women with "a carcinoma *in situ* component recorded at the time of their primary surgery", and suggested that the problem partly relates to difficulties in identifying the extent, rather than just the presence, of carcinoma *in situ*, "because many such tumours are multifocal". They suggest that more thorough use of ultrasound imaging could help decrease reoperation rates.

Some surgeons are experimenting with new tools to help them locate the margins of the tumour while they are operating. Marc Thill, head of the Department of Gynaecology and Obstetrics at the Agaplesion Markus Hospital, in Frankfurt, published a report in *The Breast* in 2011 (vol 20, pp 579–580) on the impact on reoperation rates of using a radiofrequency spectroscopy device while operating on patients with DCIS.

MarginProbe, manufactured by the US company Dune Medical Devices, involves a disposable hand-held probe and a console to detect differences in dielectric properties between normal and malignant breast tissue. Using their historical objective of 5 mm clear margins, in a study of 22 patients, use of the device lowered his department's re-excision rate, from 38.8% to 18%. In line with ongoing discussions about changing to a 2 mm margin, Thill also calculated the re-excision rate using 2 mm clear margins as the threshold, which would have reduced the re-excision rate to 14%. Thill now hopes to extend it to other types of breast cancer, and says he knows of about 11 other centres in Europe that are also using the device.

There are problems associated with the device, however; in particular its cost. The console costs around €28,000, with a further €600 for each probe, which can only be used for a single operation.

There are also questions about its value in younger women who have denser breasts, where the device may have more trouble distinguishing malignant from healthy tissue, leading to false-positive readings. "I think there may be differences in the results when MarginProbe is used in young patients, with a tumour that is right behind the nipple where the most dense tissue is located," says Thill. A further analysis is expected soon, which may shed more light on its usefulness in younger patients.

In Thill's department they calculated that, although the MarginProbe was expensive, it saved money in terms of the length of operations (surgeons' and other staff's time) and avoiding reoperations. Measuring all the margins of the specimen intraoperatively takes only three to five minutes with the MarginProbe, enabling further re-excisions to be performed as part of the same operation. However, the way breast cancer operations and reoperations are funded vary from country to country, and, therefore, the cost-effectiveness will vary too.

How good is your surgeon?

Right now, says Dixon, what is needed are international guidelines on surgical margins that are enforceable, together with systems for checking the performance of departments and individual surgeons.

"There should be national and international guidelines on how breast cancer is managed, and these guidelines should be stricter. Part of the problem with guidelines is that, while it's true that doctors should have the freedom to do what they think is right for an individual patient, they shouldn't have an authority to do something on a regular basis that is outwith guidelines. There should be a lot more emphasis on adherence to guidelines.

"We already collect a lot of data in the UK and we can identify units that fall consistently outwith two and even three standard deviations of everyone else in the UK. The problem is we have no real mechanism to find out why that centre is so different. There may be an explanation. If there is no adequate reason for why they fall outwith what everyone else is doing, then there may be a need for re-education so that these outliers can be brought into the fold. It is what patients expect and deserve.

"There has to be change, because the days of individual surgeons getting away with what they think is right are gone. It's time to follow the evidence and to protect the patient, to make sure that a patient, regardless of where they live, gets the same standard of care in all parts of the country." ■