

„To clip or not to clip. That is no question!”

Marianne Camille Aznar, PhD; Clinical trial service unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK

marianne.aznar@ndph.ox.ac.uk

Icro Meattini, MD; Radiation Oncology Unit, Oncology Department; Azienda Ospedaliero Universitaria Careggi – University of Florence, Florence, Italy

icro.meattini@unifi.it

Philip Poortmans, MD, PhD; Department of Radiation Oncology, Institut Curie, Paris, France.

philip.poortmans@curie.fr

Petra Steyerova MD, Breast cancer screening and diagnostic center, Clinic of Radiology, General University Hospital Prague, Prague, Czech Republic

Lynda Wyld MB.ChB, PhD, FRCS. Department of Oncology and Metabolism, University of Sheffield and Jasmine Breast Unit, Doncaster and Bassetlaw Teaching Hospital NHS Foundation Trust, Doncaster, UK.

L.wyld@sheffield.ac.uk

Editorial

Breast conservation surgery (BCS) followed by radiation therapy (RT) is the local treatment of choice for an increasing percentage of women with breast cancer (BC) ^{1,2}. Surgical techniques for contemporary breast conservation are sophisticated and sensitive to aesthetic considerations. In most cases of straightforward small volume excisions, the breast parenchyma is carefully closed (level 1 oncoplastic procedures). In addition, the skin incision is often placed remote from the tumour in a cosmetically optimal location. In more challenging cases, where resection volumes are larger or more extensive breast reshaping is required, the tumour bed margins may be substantially repositioned within the breast volume on a variety of dermoglandular pedicles, with margins often separated both from each other and from the surgical scars (level 2 oncoplastic procedures) ³.

In parallel, RT for breast conservation has evolved significantly in the last few decades, striving to minimise the volume of tissue irradiated to reduce late normal tissue toxicity to a minimum. Accelerated partial breast irradiation (APBI) has become a valid alternative to whole breast irradiation in selected early stage BC ⁴⁻⁶ but its successful implementation relies on the accurate definition of the tumour bed.

Identifying the tumour bed, which does not necessarily equate with the lumpectomy cavity, is a very challenging process: reliance on the skin scar and seroma cavity has been shown to be inaccurate even in the case of standard BCS, resulting in poor localization of the target volume in over half of cases ⁷. Surgical clips assist in identification of the lumpectomy cavity, improving surgical bed visualization on CT scan ^{8,9} but delineations based on these clips or on the seroma may differ, both in volume and in location ^{7,10,11}. Re-arranging breast tissue, in order to produce a better cosmetic outcome, may further hinder the radiation oncologist's ability to identify the tumour bed reliably. Hence, the success of targeted RT strategies, such as APBI, may be jeopardised unless surgeons and radiation oncologists work closely together to ensure that the tumour bed can be reliably identified.

This close multidisciplinary collaboration should involve good operative descriptions of the surgery, especially when complex level 2 procedures are used, with detailed diagrams and marking of the tumour bed using standardised protocols. Whilst many surgeons now do this, there are no generally accepted guidelines in widespread use across Europe, which impairs RT targeting. Even in countries such as the UK and The Netherlands, where adoption of oncoplastic techniques is very advanced and formal training and/or guidelines are available, these guidelines mention multidisciplinary work but make no reference to the application of clips into BCS cavities let alone specify how they should be placed ^{12,13}.

Several approaches may facilitate reliable identification of the tumour bed. The challenge lies in translating geometrical information from one medical specialty to another: between radiology and surgery in the first instance, and between surgery and radiation oncology in the second instance. Before surgery, the radiologist should strive to provide all imaging information as well as a clear interpretation of the images. Mammography and/or tomosynthesis plus ultrasonography usually provide sufficient information necessary for clinical decisions, however preoperative MRI, especially with multiplanar and 3D reconstructions, can help determine eligibility for the planned procedure, identify additional areas for resection and give surgeons a clearer idea about the size, distribution and localization of the pathology, especially in cases of extensive disease ¹⁴. Correct preoperative marking of the whole extent of the disease helps in translating the information from images to the surgeon, which is especially valuable in cases with extensive disease. Similarly, when translating information about the tumour location between surgery and radiation oncology, a detailed knowledge of the surgical procedure (type of surgery, number and placement of clips, site of the skin scar), followed by the details of the pathology report including the tumour free margins in the six main directions is essential ¹⁵. Clips need to be fixed to the tumour bed during the surgical procedure before performing any breast tissue rotation¹⁵¹⁶: while in theory six clips should be used to represent the boundaries of resection in the six main directions, in clinical practice, at least four clips are recommended.

In summary, we propose the following recommendations be adopted by breast surgeons and radiation oncologists:

1. Breast surgeons should follow the Groupe Européen de Curiethérapie- European Society of Radiotherapy and Oncology (GEC-ESTRO) guidelines for the positioning of surgical clips [12,13].

2. Breast surgeons should participate in or at least observe the technical application of boost/APBI target volume delineations after various types of lumpectomy as part of their training in breast surgical oncology, as well as part of continuous medical education so they understand the technical issues and the importance of bed marking.

3. Radiation oncologists should participate in or observe various types of lumpectomy procedures (level 1 and 2 oncoplastic procedures) as part of their training in breast radiation oncology, as well as part of continuous medical education.

This would ensure optimal multidisciplinary collaboration and optimal targeted treatment in the modern era of breast conservation.

Acknowledgements: MA acknowledges financial support from Cancer Research UK (grant no C8225/A21133)

References

1. Garcia-Etienne CA., Tomatis M., Heil J., et al. Mastectomy trends for early-stage breast cancer: A report from the EUSOMA multi-institutional European database. *Eur J Cancer* 2012;**13**(48):1947–56. Doi: 10.1016/j.ejca.2012.03.008.
2. van Maaren MC., de Munck L., de Bock GH., et al. 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study. *Lancet Oncol* 2016;**17**(8):1158–70. Doi: 10.1016/S1470-2045(16)30067-5.

3. Clough KB., Kaufman GJ., Nos C., Buccimazza I., Sarfati IM. Improving breast cancer surgery: a classification and quadrant per quadrant atlas for oncoplastic surgery. *Ann Surg Oncol* 2010;**17**(5):1375–91. Doi: 10.1245/s10434-010-1302-y.
4. Veronesi U., Orecchia R., Maisonneuve P., et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): A randomised controlled equivalence trial. *Lancet Oncol* 2013;**14**(13):1269–77. Doi: 10.1016/S1470-2045(13)70497-2.
5. Livi L., Meattini I., Marrazzo L., et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *Eur J Cancer* 2015;**51**(4):451–63. Doi: 10.1016/j.ejca.2014.12.013.
6. Strnad V., Ott OJ., Hildebrandt G., et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: A ran. *Lancet* 2016;**387**(10015):229–38. Doi: 10.1016/S0140-6736(15)00471-7.
7. Bedwinek J. Breast conserving surgery and irradiation: The importance of demarcating the excision cavity with surgical clips. *Int J Radiat Oncol Biol Phys* 1993;**26**(4):675–9. Doi: 10.1016/0360-3016(93)90287-6.
8. Dzhugashvili M., Pichenot C., Dunant A., et al. Surgical Clips Assist in the Visualization of the Lumpectomy Cavity in Three-Dimensional Conformal Accelerated Partial-Breast Irradiation. *Int J Radiat Oncol Biol Phys* 2010;**76**(5):1320–4. Doi: 10.1016/j.ijrobp.2009.04.089.
9. Weed DW., Yan D., Martinez AA., Vicini FA., Wilkinson TJ., Wong J. The validity of surgical clips as a radiographic surrogate for the lumpectomy cavity in image-guided

- accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys* 2004;**60**(2):484–92.
Doi: 10.1016/j.ijrobp.2004.03.012.
10. Ding Y., Li J., Wang W., et al. Displacement of the lumpectomy cavity defined by surgical clips and seroma based on 4d-ct scan for external-beam partial breast irradiation after breast-conserving surgery: A comparative study. *Br J Radiol* 2013;**86**(1030). Doi: 10.1259/bjr.20130416.
 11. Bartelink H., Bourcier C., Elkhuisen P. Has partial breast irradiation by IORT or brachytherapy been prematurely introduced into the clinic? *Radiother Oncol* 2012;**104**(2):139–42. Doi: 10.1016/j.radonc.2012.07.010.
 12. Martin L., Baildam A., Bishop H., et al. Oncoplastic breast surgery - A guide to good practice. *Ejso* 2007;**33**:S1–23. Doi: DOI 10.1016/j.ejso.2007.04.014.
 13. Cutress RI., Summerhayes C., Rainsbury R. Guidelines for oncoplastic breast reconstruction. *Ann R Coll Surg Engl* 2013;**95**(3):161–2. Doi: 10.1308/003588413X13511609957696.
 14. Hicks G., Turton P., Rajan S., Nunn A., Sharma N., Achuthan R. The role of magnetic resonance imaging in preoperative planning for patients undergoing therapeutic mammoplasty. *ISRN Oncol* 2013;**2013**:260260. Doi: 10.1155/2013/260260.
 15. Major T., Gutiérrez C., Guix B., Van Limbergen E., Strnad V., Polgár C. Recommendations from GEC ESTRO Breast Cancer Working Group (II): Target definition and target delineation for accelerated or boost partial breast irradiation using multicatheter interstitial brachytherapy after breast conserving open cavity surgery. *Radiother Oncol* 2016;**118**(1):199–204. Doi: 10.1016/j.radonc.2015.12.006.
 16. Strnad V., Hannoun-Levi JM., Guinot J-L., et al. Recommendations from GEC ESTRO Breast Cancer Working Group (I): Target definition and target delineation for accelerated or boost partial breast irradiation using multicatheter interstitial

brachytherapy after breast conserving open cavity surgery. *Radiother Oncol* 2015;**115**(3):342–8. Doi: 10.1016/j.radonc.2015.12.006.