



## Editorial

## De-escalation of loco-regional treatments: Time to find a balance



Breast cancer management has improved hugely over the last 3 decades. Following its increasing complexity, close multi- and interdisciplinary working relations between all specialists involved in breast cancer diagnosis and treatment within structured Breast Units are now being considered a mandatory condition. In fact, the success of this pioneering multimodal breast cancer management has led to similar models being adopted for other types of malignancies. The integrated management, as well as the availability of multiple therapeutic options and improvements in efficacy of systemic therapies have facilitated significant progress towards de-escalation of loco-regional treatments for breast cancer patients. Milestone trials, with the objective of improving patients' quality of life while keeping identical oncological outcomes, have demonstrated that the vast majority of patients can be offered breast conserving therapy instead of mastectomy [1,2] and sentinel node biopsy instead of axillary lymph node dissection (ALND) [3–6]. Furthermore, encouraging data have been recently published suggesting the feasibility of even total omission of surgery [7] or radiation therapy [8,9] in subsets of patients that either respond very well to primary systemic therapy or have a very low-risk of recurrences thanks to early detection and favourable biological cancer characteristics. Similarly, in parallel, a progress of individualization and better selection of patients for systemic therapies has been observed.

For this Special Issue, we have invited outstanding, international experts to provide an overview of the current situation for both surgical and radiation treatments as well as to share their view on future perspectives, taking into account the potential adverse consequences of too hasty de-escalation [10–26]. “Time to find a balance” is, in fact, the subtitle of this monographic work; a document that aims to give the reader a broader/more in-depth vision of the potential implications of this ongoing process.

We should also keep in mind that conditions continue to change over time. Current recommendations, including some of the rather dogmatic indications, are likely to be modified in the future, perhaps even in the near future. For instance, recent data from the monarchE [27] and Olympia [28] trials have raised the discussion on how to properly stage axillary lymph node status. While it took certain time for some to digest the Z0011 data, now the issue of performing ALND is opening again, solely for the purpose of providing information about the mere number of involved axillary nodes to fulfil criteria for prescription and/or reimbursement of new systemic treatments.

Additionally, in many cases patients with node-positive breast cancer at presentation have been treated with primary chemotherapy under the assumption that they would need chemotherapy anyway. This became

current practice, even when only a minimal likelihood of a major response could be foreseen, considering the biology of the tumour. Now, with ground-breaking data from randomized trials evaluating the omission of chemotherapy according to genomic testing [29,30], biologically low-risk patients with clinically node-positive disease at presentation are more frequently operated upfront. These results open the door to additional questions on upfront axillary surgery which seemed to be outdated until recently: should we go for a traditional anatomical ALND procedure? Should we perform a pragmatic less-invasive axillary sampling accepting its well-known limitations? Should we consider a TAXIS-like approach [31] excising just overt macroscopic disease and leaving radiation treatment to eradicate micrometastatic disease? Which is the role of regional nodal radiation therapy after less-extensive axillary surgery and depending on the biological risk [32]?

Moreover, we should not forget about the still poorly explored universe of loco-regional treatments after primary systemic therapy. Regarding the breast, a major effort should be made to reduce the number of patients receiving unnecessary mastectomies, especially considering the outstanding results achieved with primary systemic treatments in patients with triple-negative or HER2 positive breast cancer [33–35]. Additionally, the choice of surgery should consider the best option for the patient without pushing the rope for excessively complex oncoplastic procedures, that in some cases can cause more harm than good. Speaking about the axilla we should stress the importance of evaluating the results of the AXSANA [36], NSABP B-51 [37] and ALLIANCE A11202 [38] trials, which are expected to shed light on the management of nodal areas in patients undergoing primary systemic therapy [39]. However, possibly in line with a lack of solid data, a recent international survey has worryingly demonstrated the wide heterogeneity of surgical and radiation procedures in patients with positive nodes converting to node negative status after systemic treatment [40].

It sometimes feels that the more we look, the less we know: ever-new questions are raised, at a higher pace than answers can be provided. The recently published data from the randomized SOUND trial [41] demonstrates that SLNB can be avoided in patients with low-risk breast cancer without detrimental effects on five-years distant disease-free survival. So, should we therefore abandon SLNB entirely? Or just in selected patients? Or should we still perform SLNB to achieve more precise staging and eventually use this information to de-escalate other treatments?

In this complex inter-disciplinary environment, it is our duty to safeguard the continuous improvement of oncological outcomes that has been obtained over the last decades, with the hope that increasing costs

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of research and medical treatments will not undermine the widest accessibility of optimal breast cancer management. And when choices have to be made, we should respect the “Pareto principle” that 80 % of the results can be obtained with just 20 % of the efforts, highlighting the importance of education, accessibility and optimal multi- and interdisciplinary collaboration in Breast Units [42].

It is also our responsibility to continue down this path that has been described as “de-escalation” for quite some time. However, we should remember that de-escalation is just a quantitative term that we use to describe personalized care, for which expected risks and benefits of all treatment options should always be weighted. As such, it should not be considered as a black and white process, but rather as a stepwise fine-tuning towards more personalized selection, extent and especially combination of treatments, in which the interaction of loco-regional with systemic treatments on outcomes plays a huge role [43].

References

[1] Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002 Oct 17;347(16):1227–32.

[2] Fisher B, Redmond C, Poisson R, Margolese R, Wolmark N, Wickerham L, et al. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1989 Mar 30;320(13):822–8.

[3] Veronesi U, Paganelli G, Viale G, Luini A, Zurrada S, Galimberti V, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med* 2003 Aug 7;349(6):546–53.

[4] Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol* 2010 Oct;11(10):927–33.

[5] Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, et al. Effect of axillary dissection vs No axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis. *JAMA* 2017 Sep 12;318(10):918.

[6] Bartels SAL, Donker M, Poncet C, Sauv  N, Straver ME, van de Velde CJH, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer: 10-year results of the randomized controlled EORTC 10981-22023 AMAROS trial. *J Clin Oncol* 2023 Apr 20;41(12):2159–65.

[7] Kuerer HM, Smith BD, Krishnamurthy S, Yang WT, Valero V, Shen Y, et al. Eliminating breast surgery for invasive breast cancer in exceptional responders to neoadjuvant systemic therapy: a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2022 Dec;23(12):1517–24.

[8] Kunkler IH, Williams LJ, Jack WJL, Cameron DA, Dixon JM. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol* 2015 Mar;16(3):266–73.

[9] Whelan TJ, Smith S, Nielsen TO, Parpia S, Fyles AW, Bane A, et al. LUMINA: a prospective trial omitting radiotherapy (RT) following breast conserving surgery (BCS) in T1N0 luminal A breast cancer (BC). *J Clin Oncol* 2022 Jun 10;40(17 suppl). LBA501–LBA501.

[10] van Hemert AKE, van Duijnhoven FH, Vrancken Peeters MJTFD. This house believes that: MARI/TAD is better than sentinel node biopsy after PST for cN+ patients. *Breast* 2023 Oct;71:89–95.

[11] Beltran-Bless AA, Kacerovsky-Strobl S, Gnant M. Explaining risks and benefits of loco-regional treatments to patients. *Breast* 2023 Oct;71:132–7.

[12] Brunt AM, Haviland JS. Hypofractionation: the standard for external beam breast irradiation. *Breast* 2023 Jun;69:410–6.

[13] Machiels M, Oulkadi R, Tramm T, Stecklein SR, Somaiah N, De Caluw  A, et al. Individualising radiation therapy decisions in breast cancer patients based on tumour infiltrating lymphocytes and genomic biomarkers. *Breast* 2023 Oct;71:13–21.

[14] Meattini I, de Oliveira Franco R, Salvestrini V, Hijal T. Partial breast irradiation. *Breast* 2023 Jun;69:401–9.

[15] Tramm T, Kaidar-Person O. Optimising post-operative radiation therapy after oncoplastic and reconstructive procedures. *Breast* 2023 Jun;69:366–74.

[16] Dzhughashvili M, Veldeman L, Kirby AM. The role of the radiation therapy breast boost in the 2020s. *Breast* 2023 Jun;69:299–305.

[17] Bonci EA, Anacleto JC, Cardoso MJ. Sometimes it is better to just make it simple. De-escalation of oncoplastic and reconstructive procedures. *Breast* 2023 Jun;69:265–73.

[18] Banys-Paluchowski M, Rubio IT, Ditsch N, Krug D, Gentilini OD, K hn T. Real de-escalation or escalation in disguise? *Breast* 2023 Jun;69:249–57.

[19] Boersma LJ, Mjaaland I, van Duijnhoven F. Regional radiotherapy after primary systemic treatment for cN+ breast cancer patients. *Breast* 2023 Apr;68:181–8.

[20] Pfob A, Heil J. Artificial intelligence to de-escalate loco-regional breast cancer treatment. *Breast* 2023 Apr;68:201–4.

[21] Galimberti V, Ribeiro Fontana SK, Vicini E, Morigi C, Sargenti M, Corso G, et al. This house believes that: sentinel node biopsy alone is better than TAD after NACT for cN+ patients. *Breast* 2023 Feb;67:21–5.

[22] Reimer T. Omission of axillary sentinel lymph node biopsy in early invasive breast cancer. *Breast* 2023 Feb;67:124–8.

[23] Beck AC, Morrow M. Axillary lymph node dissection: dead or still alive? *Breast* 2023 Jun;69:469–75.

[24] Pfob A, Dubsy P. The underused potential of breast conserving therapy after neoadjuvant system treatment – causes and solutions. *Breast* 2023 Feb;67:110–5.

[25] Heidinger M, Knauer M, Tausch C, Weber WP. Tailored axillary surgery – a novel concept for clinically node positive breast cancer. *Breast* 2023 Jun;69:281–9.

[26] Chua B. Omission of radiation post breast conserving surgery. *Breast* 2024 February;73:103670.

[27] Johnston SRD, Toi M, O’Shaughnessy J, Rastogi P, Campone M, Neven P, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a pre-planned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol* 2023 Jan;24(1):77–90.

[28] Geyer CE, Garber JE, Gelber RD, Yothers G, Taboada M, Ross L, et al. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. *Ann Oncol* 2022 Dec;33(12):1250–68.

[29] Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med* 2018 Jul 12;379(2):111–21.

[30] Kalinsky K, Barlow WE, Gralow JR, Meric-Bernstam F, Albain KS, Hayes DF, et al. 21-Gene assay to inform chemotherapy benefit in node-positive breast cancer. *N Engl J Med* 2021 Dec 16;385(25):2336–47.

[31] Weber WP, Matrai Z, Hayoz S, Tausch C, Henke G, Zwahlen DR, et al. Tailored axillary surgery in patients with clinically node-positive breast cancer: pre-planned feasibility substudy of TAXIS (OPBC-03, SAKK 23/16, IBCSG 57-18, ABCSG-53, GBG 101). *Breast* 2021 Dec;60:98–110.

[32] Taylor C, Dodwell D, McGale P, Hills RK, Berry R, Bradley R, et al. Radiotherapy to regional nodes in early breast cancer: an individual patient data meta-analysis of 14 324 women in 16 trials. *Lancet* 2023 Nov;402(10416):1991–2003.

[33] Schmid P, Cortes J, Dent R, Pusztai L, McArthur H, K mmel S, et al. Event-free survival with pembrolizumab in early triple-negative breast cancer. *N Engl J Med* 2022 Feb 10;386(6):556–67.

[34] Gianni L, Pienkowski T, Im Y-H, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomized, multicenter, open-label, phase 2 trial. *Lancet Oncol* 2012;13(1):25–32.

[35] Dubsy P, Pinker K, Cardoso F, Montagna G, Ritter M, Denkert C, et al. Breast conservation and axillary management after primary systemic therapy in patients with early-stage breast cancer: the Lucerne toolbox. *Lancet Oncol* 2021 Jan;22(1):e18–28.

[36] Banys-Paluchowski M, Gasparri M, de Boniface J, Gentilini O, Stickeler E, Hartmann S, et al. Surgical management of the axilla in clinically node-positive breast cancer patients converting to clinical node negativity through neoadjuvant chemotherapy: current status, knowledge gaps, and rationale for the EUBREAST-03 AXSANA study. *Cancers* 2021 Mar 29;13(7):1565.

[37] Mamounas EP, Bandos H, White JR, Julian TB, Khan AJ, Shaitelman SF, et al. Loco-regional irradiation in patients with biopsy-proven axillary node involvement at presentation who become pathologically node-negative after neoadjuvant chemotherapy: primary outcomes of NRG oncology/NSABP B-51/RTOG 1304. *Abstr. In: San Antonio breast cancer symposium; 2023. GS02. 07.*

[38] A randomized phase III trial evaluating the role of axillary lymph node dissection in breast cancer patients (cT1-3 N1) who have positive sentinel lymph node disease after neoadjuvant chemotherapy. *ClinicalTrials.gov* ID: NCT01901094.

[39] Kaidar-Person O, Pfob A, Gentilini OD, Borisch B, Bosch A, Cardoso MJ, et al. The Lucerne Toolbox 2 to optimise axillary management for early breast cancer: a multidisciplinary expert consensus. *EclinicalMedicine* 2023 Jul;61:102085.

[40] Gasparri ML, de Boniface J, Poortmans P, Gentilini OD, Kaidar-Person O, Banys-Paluchowski M, et al. Axillary surgery after neoadjuvant therapy in initially node-positive breast cancer: international EUBREAST survey. *Br J Surg* 2022 Aug 16;109(9):857–63.

[41] Gentilini OD, Botteri E, Sangalli C, Galimberti V, Porpiglia M, Agresti R, et al. Sentinel lymph node biopsy vs No axillary surgery in patients with small breast cancer and negative results on ultrasonography of axillary lymph nodes: the SOUND randomized clinical trial. *JAMA Oncol* [Internet]; 2023. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3773364>.

[42] <https://www.sciencedirect.com/topics/engineering/pareto-principle>.

[43] Poortmans P. Postmastectomy radiation in breast cancer with one to three involved lymph nodes: ending the debate. *Lancet* 2014 Jun;383(9935):2104–6.

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