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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].

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