

LETTER TO THE EDITOR

Postoperative breast radiotherapy after neoadjuvant chemotherapy: which uncertainties still remain?

Filippo Alongi¹, Francesco Ricchetti¹, Alba Fiorentino¹, and Stefania Gori²

¹Radiation Oncology Department, and ²Medical Oncology Department, Sacro Cuore-Don Calabria Hospital, Negrar (Verona), Italy

The rationale of neoadjuvant chemotherapy is to achieve a high rate of response in patients with locally advanced breast cancer. It also allows earlier assessment of the sensitivity to antineoplastic drugs based on tumor shrinkage. Obviously, another endpoint of the neoadjuvant approach is to spare as many patients as possible from mastectomy, guaranteeing higher rates of breast-conserving surgery in this setting. The potential advantage in terms of micrometastatic disease control is also advocated, even if no data support this theory as yet¹.

Rastogi *et al.*² have shown that pathological complete response after neoadjuvant chemotherapy is a prognostic factor for increased survival, especially in patients with adverse prognostic factors including grade 3 tumors, ER-negative status and/or high Ki-67. A better ratio between tumor size and breast size seems to be a favorable factor in the modest increase in the breast-conserving surgery rates after neoadjuvant chemotherapy, as reported by the NSABP B-18 trial³.

However, there are still many concerns regarding the neoadjuvant chemotherapy approach. The first is the lack of upfront pathological staging, also considering that current imaging is not a reliable surrogate and that the risk of under- or overestimation may not be negligible. The second relevant issue regards the surgical procedure: obtaining a “real” conservative approach without the clear identification of the site and extent of disease at the time of resection without clip placement prior to chemotherapy could be challenging. Margin status can also change in significance after chemotherapy because tumor shrinkage may be anisotropic. Last but not least, the determination of radiation volumes and prescription doses after neoadjuvant chemotherapy remains unclear, especially after a complete pathological response. The absence of upfront pathological evidence should be taken into account in any decisions regarding locoregional radiotherapy. Unanswered questions for radiation oncologists are: a) when to include regional nodes in the treatment volume, and b) whether a radiation boost to the surgical bed is really useful and when⁴. Definitive data on the actual outcome of radiation therapy in this setting are still lacking¹.

In the NSABP B-18 and B-27 trials, the 10-year local recurrence rate was higher for patients having a cN+ status before neoadjuvant chemotherapy and a ypN+ status after surgery. It must be underlined that regional lymph node irradiation was avoided in all patients: patients undergoing lumpectomy received breast radiation only, while patients undergoing mastectomy did not receive any radiation at all. The cumulative 10-year incidence of locoregional recurrence was 12.3% in the mastectomy group and 10.3% in the lumpectomy group, with a high rate of recurrence among patients with clinical stage \geq III disease regardless of pathological complete response. Several lines of evidence have demonstrated a beneficial effect of postoperative radiation therapy on local control and survival⁵, and extension of the irradiated volumes to the ipsilateral lymph node regions could thus have an impact on the locoregional recurrence rate⁶. Based on the findings of these 2 trials, also the possible influence of the boost remains to be seriously considered in any attempts to reduce the incidence of local recurrence.

In summary, the uncertainties regarding the volumes and doses of radiation thera-

Correspondence to: Filippo Alongi, MD, Head of Radiation Oncology Department, Sacro Cuore-Don Calabria Hospital, Negrar (Verona), Italy.
Tel +39-045-6014800;
fax +39-045-014801;
email dott.filippoalongi@gmail.com

py after neoadjuvant chemotherapy and breast surgery (conservative or not) are still not negligible and deserve more focused attention not only from radiation oncologists but all physicians working in the breast team in the era of the multidisciplinary approach⁷.

References

1. Mauri D, Pavlidis N, Ioannidis JP: Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst*, 97: 188-194, 2005.
2. Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, Margolese RG, Hoehn JL, Vogel VG, Dakhil SR, Tamkus D, King KM, Pajon ER, Wright MJ, Robert J, Paik S, Mamounas EP, Wolmark N: Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J Clin Oncol*, 26: 778-785, 2008.
3. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B: Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. *J Natl Cancer Inst Monogr*, 30: 96-102, 2001.
4. Allis S, Reali A, Mortellaro G, Arcadipane F, Bartoncini S, Ruo Redda MG: Should radiotherapy after primary systemic therapy be administered with the same recommendations made for operable breast cancer patients who receive surgery as first treatment? A critical review. *Tumori*, 98: 543-549, 2012.
5. Overgaard M, Nielsen HM, Overgaard J: Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. *Radiother Oncol*, 82: 247-253, 2007.
6. Mamounas E, Anderson SJ, Dignam JJ, Bear HD, Julian TB, Geyer CE Jr, Taghian A, Wickerham DL, Wolmark N: Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. *J Clin Oncol*, 30: 3960-3966, 2012.
7. White J, Mamounas E: Locoregional radiotherapy in patients with breast cancer responding to neoadjuvant chemotherapy: a paradigm for treatment individualization. *J Clin Oncol*, 32: 494-495, 2014.