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Pre-operative radiation therapy: the “new” targeted breast cancer treatment?

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This issue of European Journal of Cancer includes an article by Dr Riet and colleagues from Gustave Roussy Cancer Centre, Paris, describing their long-term experience of pre-operative breast radiation therapy (RT) prior to planned mastectomy [1]. Between 1970 and 1984, patients were selected for preoperative RT based on the following high-risk criteria: T2 tumours with an estimated doubling time of less than 6 months; non-resectable T3 bulky tumours; non-inflammatory T4 tumours; or clinical stage N2 axillary lymph nodes. One hundred and eighty-seven patients were treated with a slightly hypofractionated schedule of 45Gy in 18 fractions, four times a week over 34 days to the breast and nodal regions, with a higher dose to internal mammary nodes permitted. After an interval of at least 4 weeks, all patients underwent a mastectomy with axillary lymph node dissection. Primary systemic therapy was not given either concurrently or any other time before surgery. Only a third of the patients received adjuvant chemotherapy. While less than 10% of the post-menopausal patients received endocrine therapy, radiation ovarian ablation was given to premenopausal patients, representing just under half of the study population. A retrospective central histopathological review was done for receptor status determination and to determine complete pathological response, which was defined as absence of invasive or in situ carcinoma in the breast (ypT0) and axillary nodes (ypN0).

Median follow up was an impressive 32 years and the outcome results are impressive especially when taking into account the treatment limitations from an era more than three decades ago. Irradiation alone produced an overall pathological complete remission (pCR) rate of 10%, reaching 26% for triple negative cancers. The 5-, 10-, 20 and 30-year loco-regional control rates were 94%, 91%, 89% and 89%, respectively. The authors comment that these results are comparable with the Early Breast Cancer Trialist Collaborative Group meta-analysis of post-mastectomy RT in node positive patients, despite the preponderance of locally advanced disease in the Parisian cohort [2]. As expected following limited systemic treatment, the overall disease-free survival (DFS) was much lower with 10-, 20 and 30-year DFS rates of 47%, 35% and 27% respectively. Multivariate analysis highlighted triple negative subtype as an independent negative prognostic factor for loco-regional recurrence, whereas positive nodal status was prognostic for a reduced DFS.

The 30-day post-operative complication rate was 19%, only slightly higher than would be expected without preoperative RT. We might assume that this was exacerbated by a high proportion of radiation-induced skin toxicity prior to surgery, due to cobalt therapy and possibly the use of bolus material in locally advanced breast cancers? Modern radiation techniques combining hypofractionation with highly conformal and intensity-

modulated RT may reduce skin toxicity and could perhaps reduce cutaneous post-operative complications.

Undoubtedly, the most important limitation of this study is its retrospective and non-randomised nature, with data derived from the experience of a single institution. Therefore, possible biases cannot be excluded and therefore we should interpret the results with caution. Notwithstanding this, we can for sure derive useful information from this very mature dataset! Firstly, it demonstrates that RT as a sole pre-operative treatment is effective, especially in triple negative breast cancer. Secondly, it suggests that re-scheduling RT before surgery is safe and does not impact significantly on peri-operative complications, confirming therapy the 16-year results from a prospective randomised Swedish trial [3]. This is similar to what is seen in other sites such as rectal cancer, where preoperative RT is a standard of practice with excellent outcomes including minimal added toxicity [4].

The challenge is now to use the knowledge provided by this dataset to further investigate the possible benefits of pre-operative breast RT. The authors touch on a key element affecting pCR rate with pre-operative RT, being the interval between completion of RT and surgery. In this study, this was short with a mean of 34 days, whereas previous data has shown that it can take many months before obtaining the maximal response, especially for luminal A type breast cancers [5]. Clearly, it is difficult, maybe even unethical, to delay surgery without further treatment and risking tumour progression, but it might be possible to evaluate prolonging the interval using a combined approach with concomitant and/or subsequent endocrine therapy. This philosophy will be investigated in Cambridge, United Kingdom, within a feasibility study, Neo-RT that will test hypofractionated whole breast RT with a simultaneous integrated boost in 3 weeks, followed by 20 weeks of an aromatase inhibitor prior to surgery. This pilot study (in set up) will target patients with larger luminal A type breast cancer to investigate whether breast conservation surgery may be facilitated. In addition, it provides an ideal platform to investigate the *direct* effects of breast irradiation in the clinical setting and thereby increase our understanding of radiation biology at both cellular and molecular levels. Another relevant finding was that triple-negative breast cancer was associated with on the one hand a higher response rate to RT, and simultaneously higher local recurrence rates. Combining preoperative RT and chemotherapy could potentially improve local control and survival, in these tumours. At Institut Curie, Paris, in the early 2000's, this approach was tested in a prospective phase II trial in patients with cT2-3 cN0-1 breast cancer, showing a pCR rate of 27% and an overall postoperative complication rate of 19%. Five-year disease-free survival and local

control rates were 83 % and 97%, respectively [6,7]. The pCR rates could be further increased by combining RT with more intensive systemic agents to increase the synergistic effect. This approach will be tested by Institut Curie in patients with locally advanced or metastatic triple negative cancer and in non-responders to standard primary chemotherapy, by combining RT with olaparib, a PARP inhibitor. This builds on pre-clinical data demonstrating the radiosensitising effect of this class of drugs [8]. Other obvious candidates for drug-RT combinations are immunotherapy agents such as PD-1/PDL-1 and DNA damage check point inhibitors that could exploit the principles of the immune-modulatory and synthetic lethality effects of the combination, respectively [9,10].

In summary, this article serves two very different and contrasting purposes. Firstly, it allows the reader to travel back in time three decades to experience the use of pre-operative RT during an era of little or no systemic therapy. Secondly, it catapults us straight into the future whereby RT may become a highly cost-effective targeted oncological agent in combination with novel drugs for use in the preoperative breast cancer arena. Collaboration with medical oncology, surgery and basic and translational research is essential for the eventual success of this approach. These are exciting times for preoperative approaches in breast cancer and we need to watch this space!

References

1. Riet FG, Fayard F, Arriagada R, et al. Preoperative radiotherapy in breast cancer patients: 32 years of follow-up. *Eur J Cancer* 2017; this issue.
2. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014;383:2127-35.
3. Rutqvist LE, Pettersson D, Johansson H. Adjuvant radiation therapy versus surgery alone in operable breast cancer: long-term follow-up of a randomized clinical trial. *Radiother Oncol.* 1993;26:104-10.
4. Wiltink LM, Marijnen CA, Meershoek-Klein Kranenbarg E, van de Velde CJ, Nout RA. A comprehensive longitudinal overview of health-related quality of life and symptoms after treatment for rectal cancer in the TME trial. *Acta Oncol.* 2016;55:502-8.
5. Arriagada R, Mouriessse H, Sarrazin D, Clark RM, Deboer G. Radiotherapy alone in breast cancer. I. Analysis of tumor parameters, tumor dose and local control: the experience of the Gustave-Roussy Institute and the Princess Margaret Hospital. *Int. J. Radiat Oncol Biol. Phys.* 1985;11:1751-7.

6. Bollet MA, Sigal-Zafrani B, Gambotti L, et al. Pathological response to preoperative concurrent chemo-radiotherapy for breast cancer: Results of a phase II study Eur J Cancer 2006;42:2086-95.
7. Bollet MA, Belin L, Reyat F, et al. Preoperative radio-chemotherapy in early breast cancer patients: long-term results of a phase II trial. Radiother Oncol 2012;102:82-88.
8. Jang NY, Kim DH, Cho BJ, et al. Radiosensitization with combined use of olaparib and PI-103 in triple-negative breast cancer. BMC Cancer. 2015;15:89.
9. Botti G, Collina F, Scognamiglio G, et al. Programmed Death Ligand 1 (PD-L1) Tumor Expression Is Associated with a Better Prognosis and Diabetic Disease in Triple Negative Breast Cancer Patients. Int J Mol Sci. 2017;18:E459.
10. Efimova EV, Mauceri HJ, Golden DW, et al. Poly(ADP-ribose) polymerase inhibitor induces accelerated senescence in irradiated breast cancer cells and tumors. Cancer Res. 2010;70:6277-82.