Editorial

Experience with intraoperative radiotherapy for breast cancer: the Geneva University Hospital's experience

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Background

Breast conserving surgery along with adjuvant radiotherapy is effective in terms of local control and survival for early-stage breast cancer (1). External beam radiotherapy (EBRT) following breast conserving surgery has been shown to improve survival by preventing local recurrence, in the Early Breast Cancer Trialists' Collaborative Group meta-analysis (2). Standard radiotherapy typically requires numerous fractions over a 3–5 week period and is performed weeks or months after surgery or chemotherapy. Partial breast irradiation (PBI) techniques, including intraoperative radiotherapy (IORT), have been investigated in the last decades (3,4). IORT is delivered at the same time as surgery, eliminating the need for numerous hospital visits in some selected cases. IORT for early breast cancer with the Intrabeam® system (Carl Zeiss, Oberkochen, Germany) has been shown to be non-inferior to EBRT in reducing local recurrence in a randomized phase III trial, the Targeted Intraoperative Radiotherapy-A (TARGIT-A) trial (5,6). The Intrabeam® radiotherapy system comprises of a miniature X-ray source that produces low energy photons (50 kV) delivered directly to the tumor bed. After surgical excision of the tumor, a reusable spherical applicator is fixed to the end of the source and placed in the tumor bed in order to obtain a homogeneous dose distribution to the surrounding breast tissues. A purse string suture is used to conform the target breast tissue to the surface of the applicator sphere. The time required for the entire procedure is 20 to 45 min, depending on the diameter of applicator required for a specific tumor bed. Results from the TARGIT-A trial demonstrated that careful patient selection and IORT can achieve good local control after breast conserving surgery.

The American Society for Radiation Oncology (ASTRO) created a task force to provide guidance for the application of PBI outside of a clinical trial (7). The ASTRO Consensus Panel proposed three patient groups for off-protocol PBI: a suitable group, for whom PBI is acceptable; a cautionary group, for whom caution should be applied; and an unsuitable group, for whom PBI is not considered appropriate. Based on the same rationale, the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) Breast Cancer Working Group recommended PBI outside clinical trials only if strict patient selection criteria are applied including only low-risk early breast cancers (8). Neither ASTRO nor GEC-ESTRO considered specifically IORT. The UK National Institute for Health and Care Excellence (NICE) has published draft guidance on the use of Intrabeam® radiotherapy as a treatment option for people with early breast cancer but they have decided not to issue final guidance until further (unspecified) evidence is available (9). In the TARGIT-A trial, the median follow-up duration was 2 years and 5 months in the whole trial population and 5 years follow-up in the so-called "earliest cohort" was only 18% (5), and that is why some clinicians would prefer to wait until the 5-year follow-up data are available.

The TARGIT-A trial also demonstrated a trend towards an improvement in overall mortality in women who received IORT compared to those who received EBRT, whilst non-breast cancer related deaths were fewer in the IORT arm. These findings have now been confirmed by a recent meta-

analysis demonstrating the use of PBI instead of EBRT in selected patients' results in a lower 5 year non-breast cancer and overall mortality, amounting to a 25% reduction in relative terms (10). The first analysis of the TARGIT-A trial, published in June 2010, showed a 4-year clinically relevant toxicity rate of about 3% in both arms, but patients receiving IORT were less likely to experience radiotherapy related complications and toxicity measured by Radiation Therapy Oncology Group (RTOG) scale.

Welzel and colleagues (11) from the University Medical Centre Mannheim, Germany assessed radiation-related quality of life (QoL) parameters in the first 123 women from a single centre participating in the TARGIT-A trial by using the Quality of Life Questionnaire C30 (QLQ-C30, version 3) and the Breast Cancer Module (QLQ-BR23) of the European Organisation for Research and Treatment of Cancer (EORTC). They concluded that patients given IORT alone reported less pain, breast and arm symptoms compared to those who were given EBRT. Hoeller *et al*. (12) compared the RTOG and the Late Effects Normal Tissue Task Force Subjective, Objective, Management, and Analytic (LENT/SOMA) scores amongst breast cancer patients, concluding that LENT/SOMA scores seemed to be a better tool than the RTOG scale for grading late toxicities, because the LENT/SOMA scale tends to upgrade skin toxicities compared to the RTOG score (13).

The Geneva University Hospital's experience

First year's experience with IORT at the Geneva University Hospital has been recently reported by Vinh-Hung and his colleagues (14). Authors have retrospectively reviewed a dataset of a cohort of women who received 20 Gy of IORT with the Intrabeam® system concurrently with breast conserving surgery between February 2012 and January 2013. A total of 52 women were treated but only 34 patients (65%) were treated with IORT alone since 18 patients (35%) received IORT followed by additional hypofractionated EBRT of 40–47.25 Gy in 15–21 fractions. IORT alone was delivered to patients deemed at low risk according to GEC-ESTRO recommendations for accelerated partial breast irradiation rather than applying the TARGIT-A trial inclusion criteria. The inclusion criteria used in this series were: age ≥50 years, tumor size ≤3 cm, invasive carcinoma other than lobular, unifocal tumor, absence of lymphovascular invasion, absence of extensive *in situ* component, clear margins ≥2 mm, pN0 or pN1mi.

Vinh-Hung and his colleagues aimed to evaluate early breast and skin toxicities after one year of experience with the Intrabeam® system. Toxicity was retrospectively scored from the records at two time points: for all patients, at the first follow-up about four weeks post-operatively; and at second follow-up, only for patients who received additional EBRT, at six weeks after radiation treatment. The toxicity scoring used was the LENT/SOMA system (15,16). Authors reported grade 2 lung toxicity (cough, dyspnea and chest discomfort) in 6 of 52 patients (11.5%). Grade 3 early breast and skin toxicities, consisting of seroma, were found in 13 of 52 patients (25.0%), whilst 3.8% of patients experienced grade 4 toxicity after IORT alone. Amongst women who were given IORT as a boost followed by EBRT, relevant grade 3 breast and skin toxicity rate was about 11.0%.

Vinh-Hung and colleagues presented results of a case series from a single centre. The study was retrospective and therefore recollection biases might have influenced data analysis. Patients were not randomized. The study lacked a control group and was small. Furthermore, 35% of patients received additional EBRT (compared to 15% observed in the IORT arm of the TARGIT-A trial), demonstrating a lack of confidence probably related to the introduction of a novel technique. The follow-up was short with a median follow-up for early toxicity evaluation of 27 days (range 13 to 70 days post-operatively), resulting in heterogeneous data. Patients examined on day 13 were more likely to have early complications, such as hematoma or seroma, compared to patients seen on day 70. Furthermore, early complications such as seroma, hematoma and wound dehiscence were common after breast conserving surgery alone and therefore it was difficult to estimate the specific impact of additional IORT treatment.

Vinh-Hung and colleagues used the LENT/SOMA scales to assess early breast and skin toxicities treatment effect estimates within the first year, retrospectively. There are other scoring systems used to report adverse events following radiotherapy. The most common is the Common Terminology Criteria of Adverse Events (CTCAE) defined by the EORTC and the RTOG. LENT/SOMA scales have been in use since 1995 and are usually employed for late toxicity assessment. Generally late toxicity is classified as toxicity occurring 90 days or more after treatment. With LENT/SOMA tables, it is possible to achieve a high level of objectivity, through the subjective tool to measure organ-related toxicities after radiotherapy (17). It gives objective and subjective opinions about complications. LENT/SOMA criteria seem to be more accurate than RTOG scale alone in grading and recording radiation toxicity, but only at a late

stage. The response of each organ or tissue included in the irradiated volume is assessed by four separate criteria within the LENT/SOMA scales: subjective symptoms, objective signs, management of signs and symptoms and the findings of special analytical investigations. In this scoring system, all four aspects play a role in defining the overall level of late radiation toxicity. The grades vary with time after radiotherapy and need to be re-recorded each time when a patient is seen in follow-up. The LENT/SOMA is a patient-scored symptom questionnaire and also overlaps with the more well recognized EORTC QLQ-C30, a QoL tool (18,19).

Neither cosmetic outcomes nor QoL have been assessed in the Geneva Hospital series. Heart toxicity has not been recorded and pulmonary function tests have not been reported despite the observed 11.5% of patients with grade 2 lung toxicity. Their results suggest that IORT followed by EBRT may increase grade 1 and 2 breast and skin toxicity, whilst grade 3 and 4 are reduced when IORT is followed by EBRT. The secondary outcomes of the TARGIT-A trial were measures of local toxicity or morbidity assessed from data recorded on the complication form, which contained a pre-specified checklist: hematoma, seroma, wound infection, skin breakdown, delayed wound healing, RTOG (version 2.0) toxicity grade 3 or 4 for dermatitis, telangiectasia, pain in irradiated field, or other. Vaidya *et al*. (6) specifically analyzed seroma requiring more than three aspirations, wound infections requiring intravenous antibiotics, any complications requiring surgical intervention, or RTOG toxicity grade more than 2. Skin breakdown or delayed wound healing or RTOG grade more than 2 was classified as major toxicity. The percentage of complications was 17.6% compared to 15.5% of complications after EBRT. In the Geneva Hospital series, breast and skin toxicities were about 25% and were not clearly listed as expected (i.e. seroma was generally and superficially defined as "the most frequent" toxicity and scored as grade 3). The authors conclude that at one month after IORT for breast cancer, only mild to moderate toxicities have been observed but the early radiation-related toxicities have been evaluated with an inappropriate tool.

Conclusions

In the treatment of breast cancer, the therapeutic benefit of radiotherapy has to be balanced against potential harmful side-effects. As cancer treatment becomes more effective and survival improves, the importance of morbidity and QoL will increase even further. Very few studies have investigated QoL after IORT (11). IORT for breast cancer has been shown to be associated with acceptable rates of local toxicities in the TARGIT-A trial. Complications were lower in the IORT arm compared to the EBRT group as reported by Vaidya *et al*. (6) and Welzel *et al*. (11). The Geneva Hospital series confirm this trend.

IORT is a viable alternative option for women with early invasive breast cancer who meet particular criteria and accept the pros and cons of a single fraction of intraoperative radiation treatment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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