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Original Article

# Integrated breast conservation and intraoperative radiation therapy

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SUMMARY

The introduction of innovative radiotherapy approaches for early breast cancer patients is rapidly changing the radiation oncologists' attitude and their expectations to obtain a good local control while decreasing morbidity therefore improving patient's quality of life. Intraoperative radiotherapy is a very attractive treatment modality in the multidisciplinary approach to breast conservation as is testified by the rapidly growing number of patients accrued in numerous studies all over Europe since 2000.

A major advantage of intraoperative radiotherapy in breast cancer treatment is the administration of a large dose of radiation directly to the tumour bed, avoiding the possible geographic miss. Accurate localization and precise definition of the tumour bed volume is essential to achieve maximal efficacy in terms of local control while minimizing unnecessary damage to the normal breast tissue. Intraoperative radiotherapy reduces radiation exposure of the skin, lung, heart and normal subcutaneous tissues thus contributing to the low incidence of side effects and the generally excellent cosmetic results.

Compared to other intraoperative techniques, the superiority of intraoperative radiotherapy appears to be the high homogeneity of dose distribution. The linear quadratic model used to calculate the biologic equivalent dose of intraoperative radiotherapy treatments for both tumour and normal tissue effects, is not considered totally reliable for large dose per fraction. The main concern is the potential increase in severe late side effects. Conversely, we expect an enhanced local control due to the radiobiologic efficacy of a large single dose delivered soon after tumour excision, with an immediate cell killing effect over any potential microscopic disease. The advantage of shortening the overall treatment time is that it avoids any delay in the administration of chemotherapy. The safety of intraoperative radiotherapy as a treatment modality in the context of breast conservation has been proved but conclusive data on local control and survival are expected from long term results of the ongoing studies.



## Introduction

Breast-conserving surgery followed by whole breast irradiation with an additional boost to the tumour bed is widely accepted as the standard treatment of early stage breast cancer. Six randomized trials established the equivalence of breast-conserving surgery followed by radiotherapy to mastectomy. A recent EBCTCG meta-analysis confirmed the role of radiotherapy after lumpectomy demonstrating that breast irradiation reduced the 5-year local relapse (LR) rate from 26% to 7%.[1,2] Conventional treatment is delivered to the whole breast via two tangential fields of photons, followed by a regional dose to the tumour bed typically using an en face electron field. With the rapid technological advances in radiotherapy, more complex techniques such as 3D conformal radiotherapy (3DCRT) and intensity modulated radiotherapy (IMRT) are now widely available. These sophisticated modalities are applied to the treatment of early breast cancer in order to minimize morbidity, particularly to cardiac and pulmonary tissue, and to improve cosmesis.[3] Partial Breast Irradiation (PBI) consists of the irradiation of the site of surgical excision and adjacent tissues only. The rationale comes from the results of a number of long term studies reporting that LR occur mostly in the primary tumour site. The concept of PBI is driving the modern evolution of minimum effective treatment in breast radiotherapy, opening the way to new models of breast conservation. Since breast cancer is one of the most commonly treated pathologies in the radiotherapy departments, any change in the approach of the adjuvant treatment has a great impact on the available resources. The hot topic is whether shorter more intensive regimens, including PBI, have similar efficacy to the standard fractionation schedule.[4]

## Partial breast irradiation background

Different methods of PBI are under investigation, including brachytherapy, intraoperative RT (IORT) and 3DCRT in order to

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establish the impact on local control and survival.[5] A key issue is whether PBI is adequate or if the entire breast needs to be irradiated after breast-conserving surgery. There are no conclusive data up to date to support or not the use of PBI. Uncertainties in clinical outcome can be strongly influenced by patient selection and are also due to the too short follow-up time of some institutional experience, often with small numbers of patients treated, and the need for definitive results of several large randomized trials that are still currently ongoing. Among the different PBI techniques, intraoperative radiotherapy with electrons represents a very interesting approach. IORT for breast conservation is not a totally new concept. The early experiences started in the early 1990s, when a European and an American group published small series of patients treated with conservative surgery and a boost of intraoperative RT followed by whole breast radiotherapy.[6,7] The acute and intermediate toxicity was encouraging but an increasing interest developed when in 2000 the European Institute of Oncology (EIO) started a randomized phase III trial comparing conventional whole breast RT with 21 Gy full dose intraoperative RT with electrons (ELIOT).[8] The trial accrual was closed at the end of 2007, results are pending.

A major concern over modern radiotherapy is toxicity, therefore most research is directed to sophisticated approaches which allow maximum reduction of late toxicity. ELIOT offers a simple tool to avoid or minimize the irradiation of organs or structures at risk. Skin and subcutaneous tissues, moved away from the collimator, are not irradiated, and an aluminum and lead disk, placed between the gland and the pectoral muscle, protects the thoracic wall and the underlying organs such as lung and heart. The great advantage of ELIOT is that none of the critical structures typically involved in the conventional treatment fields of the breast are irradiated. Furthermore, the pectoral muscle spared from the irradiation could be used for subsequent breast reconstruction after mastectomy in case of local failure after conservative approach. For early breast cancer patients wishing breast augmentation during quadrantectomy, the delivery of IORT on a small glandular volume, sparing skin and pectoral muscle, allows to avoid the adverse effects of external radiotherapy on the prosthesis.[9] A major concern over IORT is the potential late toxicity due to the high-dose delivered in a single fraction. The dose of 21 Gy adopted at the EIO was established on the basis of a linear-quadratic model. However according to this model with long-term follow-up, a possible increase of side effects such as fibrosis or necrosis of the irradiated area is expected. In the first report of the Italian group of Trento on 47 patients treated with a single dose of 20–24 Gy, after a median follow-up of 48 months, 15 patients developed ≥G2 breast fibrosis, while asymptomatic fat necrosis was observed in 25.5% of the patients.[10] The EIO group reported on 1246 patients treated with 21 Gy full dose, observing severe fibrosis in 0.5% of the patients and mild fibrosis in 3.2%. Liponecrosis, observed in 4.7%, was easily managed with few session of clinical care.[11]

When IORT is employed just as a boost with a reduced dose, the expected rate of side effects is lower. In the updated report of the Lemanski and Merrick study, no Grade 3 fibrosis in the boost area was recorded.[12,13] Nonetheless the optimal combination for dose and fractionation for whole breast RT integrated to IORT boost has not been established and further investigational and confirmatory studies are needed.

## Definition of the target for the boost

The primary goal of breast conservation is disease control particularly in the tumour bed were the majority of LR develops.[14] An additional dose to the area of the original disease has been demonstrated to improve local control in two randomized trials.[15,16] The EORTC study recently confirmed the advantage of the boost also in histologically negative margins, especially in young patients. These findings confirm the concept of dose-response for microscopic residual disease. It is of critical importance that the optimal dose is effectively delivered to the tumour bed to achieve the highest local disease control. Accurate definition of the boost region is crucial for a correct treatment planning in order to achieve a maximal effect and minimize unnecessary damage to the normal breast tissue.[17] Usually, the boost region is defined based on clinical information, such as palpable abnormality and scars, preoperative mammography and surgical reports, but these procedures could carry a significant risk of target missing up to 23–70% of the cases,[18,19] especially when a cosmetic gland reconstruction has been performed. Landis demonstrated a large variability in the delineation of the site and size of breast lumpectomy cavity for RT planning even among senior physicians who are specialized in breast cancer.[20] A recent study demonstrated a difference of more than 1 cm in more than 50% of the patients in the definition of the isocenter of the electron field boost when it was clinically defined compared to a CT based determination.[21] Surgical clips placement assists tumour bed localization but doesn't guarantee an absolute accuracy because the lumpectomy cavity tends to shrink with time. In a study by Weed a 55% reduction in the postlumpectomy cavity volume was found when 2 CT scans acquired an average of 28 days apart were compared.[22]

When the location of the tumour bed is uncertain a large field size for the boost is usually chosen in order to compensate for the uncertainty. Nonetheless in a retrospective study from Jobsen the size of the external beam boost volume did not impact on both local control and 15-year LR free survival.[23] A possible explanation could be that the position of the isocenter is probably more important than the size of the treated field. Moreover, in the EORTC trial, the group that received the boost experienced a worse cosmetic outcome suggesting that larger boost field size could aggravate fibrosis.[24] In an observational study conducted by Reitsamer the group of patients receiving intraoperative boost of 9 Gy obtained a better local control at 5 years than the group receiving external electron boost of 12 Gy. This finding confirms the advantage of the exact knowledge of the tumour bed localization and seems to demonstrate that one cause of local recurrence could be the partial geographic miss of the target volume.[25] Indeed, long term follow up of both the American and European experiences with intraoperative boost yielded very low LR rates.[26,27]

Another advantage of IORT is the direct visualization of the tumour bed during surgery which avoids the demanding work of tumour bed reconstruction performed every time an accurate localization of the boost volume is sought during external beam radiotherapy planning.[28]

Furthermore, it is essential that the dose is prescribed to include the entire target volume. Compared with other intraoperative techniques (interstitial brachytherapy, MammoSite, Intrabeam), IORT delivers the most homogeneous dose distributions to the planning target volume. Moreover, with IORT, the average dose obtained inside the target volume is the closest to the prescribed dose with the smallest maximum value, while the surrounding healthy tissues receive the lowest average and minimum dose.[29]

## Timing of adjuvant radiotherapy

Timing between surgery and adjuvant radiotherapy traditionally has been a critical issue. Particularly in some geographic areas, the access to radiation treatment is limited by long waiting lists, therefore is now even more relevant the issue of whether or not a delay in starting RT has a detrimental effect on outcomes. Practice guidelines recommend not to exceed 8 to 12 weeks between surgery and adjuvant RT, except for patients undergoing

chemotherapy (CT).[30] According to a theoretic model, the efficacy of adjuvant therapy is reduced with time due to a increasing number of clonogenic cancer cells, even if results on local control rates from clinical studies are contradictory.[31] Based on a radiobiologic model, the risk of LR after surgery is related to the density of clonogenic tumour cells present in the surgical bed when RT is initiated. Therefore a delay in delivering RT seems to favour clonogenic tumour cell growth and may be associated with an increased risk of LR.[32,33] A recent meta-analysis of 8 observational studies performed by Herbert-Croteau led to an estimated odds ratio for LR of 1.62 (95% CI 1.21–2.16) for women treated between 9 and 16 weeks after surgery compared to those who received RT earlier. No significant impact on distant metastases and no data on overall survival were reported.[34] A study by Hershman on 24,833 women not receiving adjuvant CT found that a delay of more than 3 months in starting RT was associated with higher overall mortality (HR 1.92; 95% CI 1.64–2.24) and cancer specific mortality (HR 3.84; 95% CI 3.01–4.91).[35] A systematic review conducted by Huang concluded that 5-year LR rate was significantly higher in patients receiving adjuvant RT more than 8 weeks after surgery compared to those treated within 8 weeks. A time interval of 9–16 weeks between lumpectomy and the beginning of RT was associated with a 62% increase in the rate of LR compared with less than 8 weeks.[36]

Other retrospective reviews however did not show any impact of delayed RT on local control. Nixon observed no difference in 653 patients without lymph node involvement who did not receive CT on a cut-off of 4 weeks for the time between RT and surgery.[37] In a similar cohort of patients, Vujovic did not find any difference in terms of LR in four time intervals from 0 to more than 16 weeks.[38] However, the time spent waiting for radiotherapy could represent an additional source of anxiety that affect patient's quality of life. ELIOT, providing an efficient dose delivery immediately after the tumour excision, optimizes the biological efficacy against a possible residual tumour burden which represents an important risk factor for LR mostly in high-risk patients.[39,40] By giving a large dose in a single fraction, the same amount of neoplastic cells could be killed with a dose reduced by one-half to one-third relative to conventional fractionation. According to alpha/beta of 10 for tumour cells, a single dose of 9–12 Gy is biologically equivalent to 17–26 Gy given with conventional fractionation. The possibility to avoid accelerated repopulation of neoplastic clones in the tumour bed immediately after tumour excision could explain the good local control observed in the reported series that received intraoperative boost.[7,12,13,26,41]

## Integration of radiotherapy with the systemic treatment

The increasing number of innovative radiotherapy approaches for patients with early breast cancer led to reconsider different aspects of the integration of conservative surgery and radiotherapy. Another critical issue is represented by the temporal sequence of radiotherapy and the systemic treatment. A delay in starting RT after the end of CT might lead to higher rates of local breast recurrence. Indeed, delaying RT may allow the progression of microscopic disease beyond the limits of cure foreseen by conventional doses. Furthermore current CT regimens such as the addition of the taxanes to doxorubicin and cyclophosphamide are often longer than in the past. Despite many retrospective studies reporting contradictory data, probably due to selection biases, some evidence suggests that CT provides protection against local failure even when it causes a delay in the initiation of RT.[42,43] The update of the first prospective randomized trial designed to investigate the best sequence of treatments showed no significant difference in local and distant recurrence rates, at 10 years, between the two treatment arms although the trial was underpowered to detect small differences.[44] However in a subgroup of patients with close margins a lower LR was reported in the RT-first arm than in the RT-delayed arm (4% vs 32%). Conversely, patients with positive margins had a high rate of LR independently of the sequence of therapies (20% and 23% in the two arms respectively) indicating that a greater residual tumour burden represents an important risk factor for LR. At the present time we are unable to state if IORT performed in microscopically close or positive margins could avoid surgical radicalization without compromising local control. Probably preliminary information will come from the ELIOT randomized trial where a small subgroup of patients with positive margins that underwent IORT are actively followed.

The overview published by Bowden analyzed LR rate in 21 studies. Five of these showed a significant increase in LR rate when RT was delayed, two were of borderline significance, and 14 showed no significant difference.[45] Nonetheless, several retrospective studies showed a higher LR when the beginning of RT was delayed. Whelan's meta-analysis of RT trials showed a significant decrease in mortality among patients irradiated within 6 months since the initiation of systemic therapy.[46] In the cohort of 845 stage I women of the Herbert-Croteau study, the 20% who initiated RT more than 12 weeks after surgery had a 75% higher rate of LR compared to the 80% who started RT sooner. Delay was not associated with a difference in overall survival but the study was underpowered to detect a survival difference.[34] Benk estimated that the effect of delaying RT was 1% per month of delay.[47] One way to avoid any delay would be the concurrent administration of RT and CT; this would be an attractive approach but major concerns are the potential risk of increasing toxicity, worsening of cosmetic results and a reduction of patients' compliance to both treatments. Many studies reported an increased risk of pneumonitis,[48] impaired cosmesis,[49] and cardiac damage especially with concurrent administration of doxorubicin.[50] The development of ischemic heart disease has been correlated with the volume of heart irradiated and total radiation dose. Only two randomized clinical trials compared concomitant CT and RT with the sequential schedule.[51,52] Except for a subgroup of women with node positive disease, these trials did not show any difference in LR rate between the two treatment groups. In order to minimize the probability of severe acute toxicity induced by the concomitant treatment, different studies used various solutions: omit RT on the day of intravenous administration of CT, avoid methotrexate administration during the two cycles concomitant to RT, reduced dose-intensity of either RT or CT, or allowing only a minimal overlapping of the two treatments.[53–55] Combining IORT with conservative surgery not only reduces treatment time but avoids any delay of both local and systemic treatments. With the same purpose, at the European Institute of Oncology a non-randomised study has been conducted since 2004 with IORT as a boost followed by 13 fractions of hypofractionated external beam radiotherapy in premenopausal women. The whole breast radiotherapy starts within three weeks from surgery and is concluded in a 2.5 weeks period allowing CT to start without delay within six weeks from surgery. Available data on the first 211 patients treated, showed a high compliance to treatment: 99.5% of the patients completed the whole treatment schedule. Acute and intermediate toxicity was acceptable also in the few patients who received the first cycle of CT concomitantly to the last fractions of RT.[41]

In an increasing number of radiotherapy departments the use of a mobile IORT unit overcomes all the logistical problems associated with intraoperative RT. IORT performed with these compact accelerators can be delivered easily avoiding all the potential hazards related to the transportation of the anaesthetized patient from the operating room to the radiotherapy department as it has been traditionally performed. Furthermore these compact

linear accelerators do not require a dedicated room but can be installed and safely operated in a conventional operating suite supplied by mobile shielding.

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