

Locoregional Therapy in Breast Cancer

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Abstract

Breast cancer is the most common cancer in women. In 2004, estimates were that about 215,990 women and approximately 1,500 men in the US would be diagnosed with invasive breast cancer. Surgery and radiotherapy, either alone or combined, remain the most effective techniques to treat cancer. Surgical procedures have been clearly defined by several randomised clinical trials that demonstrated equivalent survival with breast-conservation surgery combined with radiotherapy versus mastectomy. In the last few years, in order to avoid the risk of lymphoedema caused by axillary dissection, in patients free from axillary lymph node metastases sentinel lymph node biopsy has been widely accepted as a standard of care. The use of whole-breast irradiation with or without a boost is the standard of care at present. The value of adding nodal irradiation to the breast irradiation is unproven. Local control is influenced not only by treatment modalities but also by screening programmes, allowing the possibility of identifying smaller and smaller lesions. Nowadays, local control for breast cancer is a fundamental part of treatment. The surgical approach is tailored towards conservation of the breast and good-looking cosmesis, while radiotherapy is tailored towards reduction of treated volume to reduce damage and to spare time and cost.

Keywords

Breast cancer, radiotherapy, mastectomy, conservative surgery, partial breast irradiation, adjuvant chemotherapy, screening

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At the beginning of the third millennium, one in three EU citizens will have to deal with cancer in the course of his or her life. Worldwide, the estimated number of new cancer cases is expected to rise from 10 million in 2000 to 15 million by 2020. Currently, cancer is the cause of 12% of all deaths worldwide. In the EU, over 1.5 million new cancer cases are diagnosed every year, and over 920,000 people die of cancer, the most common cancer sites being the breast and the prostate. About 90% of cured patients recover because of locoregional control; 18% of all patients die because of a primary tumour without metastases. This means that local treatment is as important as systemic therapy.

Breast cancer is the most common cancer in women. In 2004 it was estimated that 215,990 women and 1,500 men in the US would be diagnosed with invasive breast cancer. In the last decade there has been a 21% decrease in age-adjusted mortality from breast cancer.¹ The decline in mortality has been attributed to early detection of the disease and to the use of aggressive multimodality treatment leading to improved clinical outcomes.

Locoregional Treatment

Surgery and radiotherapy, either alone or combined, remain the most effective techniques to treat cancer. More than half of all cancer patients are now treated by radiation therapy (RT) thanks to the technical progress made with irradiation equipment over the last 10 years. Today a woman with early-stage breast cancer can be approached with the assumption that her breast can be spared and that therapy will be provided in a tailored and integrated fashion.

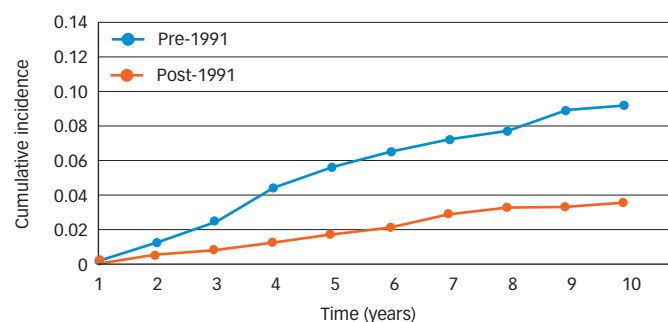
Breast Surgery

Surgical procedures have been clearly defined by several randomised clinical trials that demonstrated equivalent survival with breast conservation surgery combined with radiotherapy versus mastectomy. In a study of 701 randomised women, Veronesi et al. reported that after a follow-up of 20 years, 30 women in the group who underwent breast conservation therapy had a recurrence of tumour in the same breast, whereas eight women in the radical mastectomy group had local recurrences ($p < 0.001$). The crude cumulative incidence of these events was 8.8 and 2.3%, respectively, after 20 years. By contrast, there was no significant difference between the two groups in the rates of contralateral breast carcinomas, distant metastases or second primary cancers. After a median follow-up of 20 years, the rate of death from all causes was 41.7% in the group who underwent breast conservation surgery and 41.2% in the radical mastectomy group ($p = 1$). The rate of death from breast cancer was 26.1 and 24.3%, respectively ($p = 0.8$).²

The conservative surgical approach to a primary breast tumour involves excision of all apparent invasive cancer with clear margins of excision, including all ductal carcinoma *in situ*. The tumour is excised as a single block with several millimetres of apparently normal tissue surrounding it. Small titanium clips on the walls of the excision cavity are valuable for targeting breast irradiation.³

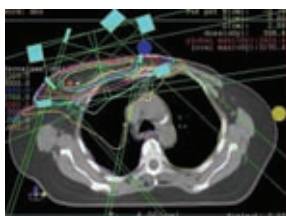
The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) study, a meta-analysis of all prospective randomised trials of

Figure 1: Cumulative Incidence Curves at 10 Years of 3,435 Breast Cancer Cases Treated at the University of Florence Radiotherapy Unit



Log-rank test $p < 0.0001$.

Figure 2: Axial View of an Accelerated Partial Breast Irradiation Treatment with Intensity-modulated Radiation Therapy, Used in the Radiotherapy Unit of the University of Florence (Phase III Randomised Clinical Trial)



locoregional therapy, demonstrated that the use of radiation after surgery significantly decreased the 15-year risk of breast cancer mortality for most women treated for breast cancer. Specifically, in the trials that investigated radiation use after breast conservation surgery, the meta-analysis demonstrated that radiation provided a 70% proportional reduction in the risk of locoregional recurrence (LRR). For patients with lymph-node-negative disease treated with breast conservation, radiation reduced the risk of LRR from 29 to 10%, and for those with lymph-node-positive disease, the LRR rates were reduced from 47 to 13%. After 15 years, these benefits translated into a 5% (lymph-node-negative) and 7% (lymph-node-positive) absolute reduction in breast cancer mortality. The survival benefits did not become evident until after five years of follow-up.⁴

However, there are some situations in which breast-conserving surgery is not possible (multicentric breast cancer, diffuse malignant microcalcification, prior breast irradiation, pregnancy or active collagen disease). Another common reason for performing mastectomy for early-stage breast cancer can be the tumour size relative to breast size, because excision to a clear margin could leave a significant deficit in breast volume or distort the shape of the breast in such a way that a better cosmetic outcome could be achieved by skin-sparing mastectomy and reconstruction. In order to avoid mastectomy, it is possible to prescribe pre-operative (neoadjuvant) chemotherapy. This approach permitted a 60% rate of breast-conservation therapy in women who would otherwise have required mastectomy.⁵ In addition, patients who received neoadjuvant chemotherapy after mastectomy are at risk of LRR related to both the initial extent of disease, defined by clinical staging, and the residual post-chemotherapy pathological extent of disease.⁶

All patients with clinical stage III breast cancer – even those demonstrating an excellent response to the pre-operative chemotherapy treatment – derive benefits from post-mastectomy radiation. McGuire et al., in a retrospective series of 226 patients treated with neoadjuvant chemotherapy who achieved a complete pathological response, reported that use of RT did not affect the 10-year rates of LRR for patients with stage I or II disease (the 10-year LRR rate was 0% for both groups). However, the 10-year LRR rate for patients with stage III disease was significantly improved with RT ($7.3 \pm 3.5\%$ with RT versus $33.3 \pm 15.7\%$ without RT; $p = 0.04$). Within this cohort, the use of RT was also associated with improved disease-specific and overall survival.⁷ Patients with lymph-node-positive disease who did not undergo neoadjuvant chemotherapy were shown to derive benefits from the use of adjuvant radiation after mastectomy as well. In this cohort, the use of radiotherapy reduced LRR from 29 to 8% and improved the 15-year breast cancer mortality rate by 5%.⁸

Surgery of the Axilla

For many years, axillary dissection was performed as a standard part of all early breast cancer treatment to provide this important staging information. In the last few years, in order to avoid the risk of lymphoedema caused by axillary dissection in patients free of axillary lymph-node metastases, sentinel lymph-node biopsy (SLNB) has been widely accepted as the standard of care. The efficacy of biopsy of the sentinel lymph nodes in identifying the lymph-node-negative axilla without axillary dissection has been clearly demonstrated by several authors. In the sentinel lymph-node era, axillary lymph-node dissection (ALND) for uninvolved axillary lymph nodes should be considered unnecessary and inappropriate.

Intra et al. reported that between January 2000 and August 2005, 3,487 of 10,031 invasive breast cancer patients consecutively operated on at the European Institute of Oncology were considered not suitable for SLNB and were directly submitted to ALND (direct ALND). In 2,875 cases (82%) a variable grade of axillary involvement was shown, whereas in 612 patients (18%) no evidence of metastatic spreading was documented in the axilla. In particular, the presence of suspicious nodes at pre-operative clinical evaluation of the axilla (191 patients), neoadjuvant treatment (188 patients), large tumour $> 2\text{cm}$ (88 patients), multifocality of disease (76 patients) and previous excisional biopsy (49 patients) were considered the most frequent contraindications to SLNB and led to an unnecessary ALND. According to the wider extension of the indications for SLNB over time, the number of unnecessary ALNDs progressively decreased from 26% (in 2000) to 9% of the direct ALNDs (in 2005). As the clinical indications for SLNB are progressively expanding to encompass most breast cancer patients with non-metastatic disease who were previously excluded, great effort should be made to avoid unnecessary ALNDs.⁹⁻¹¹

Radiotherapy

The goal of sparing the breast during surgery is substantially less likely to be accomplished without the addition of breast irradiation. The use of whole-breast irradiation (WBI) with or without a boost is currently the standard of care. The total treatment time is five to six weeks with a total dose of 50/60Gy delivered in 2Gy per fraction. Irradiation after lumpectomy is effective in reducing the risk of ipsilateral breast cancer recurrence. The 20-year update of the National Surgical Adjuvant Breast and Bowel Project B-06

reported 39.2% local failure without irradiation compared with 14.3% with irradiation.¹²

The value of adding nodal irradiation to the breast irradiation is unproven.¹³ Local control is influenced not only by treatment modalities but also by screening programmes (allowing the possibility of identifying smaller and smaller lesions). In fact, in our experience the cumulative incidence of breast relapse is 4.8%, but, considering two subpopulations (pre- and post-1991) that are significant in order to distinguish screening modalities, we found a breast relapse incidence of 10.3 and 2.1%, respectively (Fisher exact test $p=0.0001$) (see *Figure 1*).

Alternative methods of delivering radiation treatment after breast conservation surgery include accelerated WBI and accelerated partial breast irradiation (APBI). Hypofractionation is attractive for WBI or partial breast irradiation because it allows treatment to be given with fewer fractions in a shorter period of time and at a lower cost. A number of cohort studies suggest that hypofractionation may be given to the whole breast safely and with good local control. Recent randomised trials have confirmed that hypofractionated WBI is equivalent to conventional WBI in terms of LRR and cosmetic outcome.¹⁴⁻¹⁶

In women treated with conservative breast surgery, whether or not followed by radiotherapy, at least three-quarters of ipsilateral tumour relapses occur in the vicinity of the primary tumour¹⁷⁻¹⁹ within the first five to 10 years, most of which, on pathological criteria, represent local recurrences of the original primary tumour. The majority of ipsilateral relapses occurring outside the index quadrant after 10 years post-treatment have pathological features consistent with new primary tumours. Due to this biological behaviour of breast cancer, we believe that in a selected subgroup of patients it is possible to obtain the same result in terms of overall survival and local control by treating the index quadrant alone instead of the whole breast.

The technical approaches to partial breast irradiation differ widely, including multi- and single-source high-dose-rate brachytherapy, intraoperative megavoltage electrons²⁰ or kilovoltage X-rays and conformal radiotherapy with high-energy photons (see *Figure 2*).²¹

APBI seems to obtain the same results in terms of breast recurrence as standard fractionated radiotherapy. In order to show potential differences in LRR rates on the basis of the volume of breast tissue irradiated, Antonucci et al. compared patients treated with APBI with 199 patients treated with WBI. The median follow-up for surviving patients was 9.6 years (range 0.3–13.6 years). The cumulative incidence of ipsilateral breast tumour recurrences at 10 years was 5%. On matched-pair analysis, the rate of ipsilateral breast tumour recurrences was not statistically significantly different between the two groups (5%, 95% confidence interval [CI] 1.5–8.5% for APBI patients versus 4% for WBI therapy patients, 95% CI 1.3–6.7%; $p=0.48$). These data are critical in assessing the potential efficacy of APBI because only minimal data from phase III clinical trials are currently available.²²

Conclusion

Currently, local control for breast cancer is a fundamental part of treatment. The surgical approach is tailored to conservation of the breast and good-looking cosmesis, whereas radiotherapy is tailored to a reduction of the treated volume in order to reduce damage and spare time and cost. ■



Lorenzo Livi is a researcher in radiation oncology at the University of Florence, Italy. He is actively involved in the fields of breast cancer, urogenital cancer and soft-tissue sarcoma, and in the use of modern technologies in diagnostics and radiotherapy. Dr Livi specialised in radiation oncology after graduating in medicine and surgery in 1997.

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