



Loco-regional therapy and breast cancer survival: Searching for a link



Riccardo Ponzone^{a,b,*}, Michael Baum^c

^aDivision of Gynecological Oncology, Fondazione del Piemonte per l'Oncologia, Turin, Italy

^bInstitute for Cancer Research and Treatment (IRCC) of Candiolo, Strada Provinciale 142, Km. 3.95, 10060 Candiolo, Turin, Italy

^cThe Clinical Trials Group, Dept. of Surgery, University College of London (UCL), Clerkenwell Bldg, Whittington Campus, London N19 5LW, UK

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ABSTRACT

Objective: The relationship between loco-regional (LR) control and breast cancer survival was investigated with the intention of generating a new biological hypothesis to explain some of the paradoxes unaccounted for by the prevailing conceptual model of the disease.

Background: The progressive reduction of surgical aggressiveness has been accompanied by an increase of breast cancer survival mainly attributed to the adoption of adjuvant systemic therapies. More recently, it has been recognized that effective LR control may prolong the survival of breast cancer patients, although the reasons for this improvement have not yet been clearly defined.

Methods: The literature (PubMed) was reviewed for publications related to breast cancer LR treatments using the following key words: breast cancer surgery, breast cancer radiotherapy, breast cancer loco-regional control, breast cancer survival.

Results: Although breast cancer is frequently a multifocal disease, neither mastectomy nor whole breast irradiation are always mandatory to obtain adequate local control. Conversely, selected groups of patients carry a particularly elevated risk of LR relapse and require more effective treatments to be developed. True LR recurrences are associated with a decreased overall survival and this may be related to a complex relationship between circulating tumor cells, re-seeding of the primary tumor site and several metabolic effects linked to the act of surgery.

Conclusion: The prevention of LR recurrences is a major goal of breast cancer care, which requires a better understanding of the complex relationships between the primary tumor and its metastatic process.

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Introduction

The evolution of breast cancer treatment over the last century has witnessed the progressive reduction of surgical aggressiveness and the parallel increase of adjuvant systemic treatments.¹ The scientific rationale behind this evolution was the recognition that breast cancer may already be a systemic disease in a subclinical phase of its natural history. Therefore, the prevailing opinion in the medical community became that local treatments would inevitably fail to improve survival once the disease has already colonized distant sites.

The first consequence of this paradigm shift consisted in the reduction of the extent of surgery. The demonstration that breast conserving surgery plus radiotherapy versus mastectomy, as well as sentinel node dissection versus axillary dissection, are associated

with a comparable long-term survival, has provided robust experimental data in support to the concept that more focused surgery is better surgery.^{2–4}

The second consequence was a rapid adoption of adjuvant systemic treatments, which led to a substantial reduction of local and distant, relapses and ultimately improved overall survival of breast cancer patients. Over the last years, the introduction of new endocrine and cytotoxic treatments, as well as the development of biologically targeted therapies for selected subsets of patients, further reduced breast cancer mortality worldwide.^{5–7}

In this paper the available data and the new hypotheses on the relationship between loco-regional (LR) control and survival will be reviewed from the standpoint of a breast surgeon.

Methods

The literature (PubMed) was reviewed for publications focusing on breast cancer LR control and its relationship with overall survival, using the following key words: breast cancer surgery, breast cancer radiotherapy, breast cancer loco-regional control,

* Corresponding author. Institute for Cancer Research and Treatment (IRCC) of Candiolo, Strada Provinciale 142, Km. 3.95, 10060 Candiolo, Turin, Italy. Tel.: +39 011 9933036; fax: +39 011 9933440.

E-mail address: riccardo.ponzone@ircc.it (R. Ponzone).

breast cancer survival. Some of the paradoxes unaccounted for by the prevailing conceptual model of the disease were also explored with the intention of generating a new biological hypothesis to explain why LR control may prolong the survival of breast cancer patients.

Multi-centricity and local control

Holland et al⁸ in their pivotal study showed that tumor foci around the primary tumor are present in 63% of the cases; this figure was confirmed 20 years later by the analysis of 500 mastectomy specimens on large-format histological sections.⁹ The finding that multifocal disease was outside the index quadrant in the majority of cases, coupled with the clinical observation that most of local recurrences occur in the same quadrant, set the basis for the development of breast conserving surgery (BCS) and whole breast irradiation (WBI) followed by a boost to the tumor bed.¹⁰ The justification for WBI is now being challenged.

A paper published by Vaidya et al in 1996 had already suggested that the picture was actually more complex.¹¹ In a series of mastectomy specimens, they observed that the relative distribution of primary tumors and multi-centric foci (MCF) obtained by two dimensional plotting was significantly different. In fact, the primary tumor was more common in the upper outer quadrant whereas MCF were widely distributed in all four quadrants. Furthermore, taking breast volume into consideration and expressing the analysis in three dimensions, MCF were present beyond the index quadrant in half of the cases. Therefore, the authors suggested that early recurrences do not arise from MCF as most early in-breast recurrences after BCS plus WBI occur in the index quadrant with or without WBI despite the fact that the remaining quadrants harbor MCF in 50% of the cases.¹¹

The concept that surgical excision of all MCF may not be necessary is further supported by recent data on the use of magnetic resonance imaging (MRI) in the preoperative assessment of patients with primary breast cancer. A recent meta-analysis suggests that MRI detects ipsilateral additional disease in 20% of the patients as compared to conventional imaging and prompts conversion to more extensive surgery in 12.8% of the cases.¹² Nevertheless, according to the results of two multicentre randomized controlled trials, MRI does not appear to reduce reoperation rate nor to improve local recurrence-free interval rates, despite allowing more complete tumor excision through its improved diagnostic sensitivity.^{13,14} The tragedy resulting from this abuse of new imaging technology, has been the “epidemic” of bilateral mastectomy following the diagnosis of unilateral single focus disease.^{15,16} The hard won knowledge over decades of clinical trials involving 10 s of thousands of women demonstrating the safety of breast conserving surgery, has been totally ignored because of a slavish obsession with the image rather than the patient.¹⁷

Partial breast irradiation and local control

The concentration of local recurrences in the index quadrant after BCS led to the hypothesis that WBI of the preserved breast could be substituted by partial breast irradiation (PBI). Several randomized trials are underway and one has already been published, suggesting that PBI may indeed be indicated in a subset of patients at low risk of local relapse.^{18,19} Nevertheless, the same could not be true for patients with more aggressive tumors. It has been demonstrated that four distinct intrinsic subtypes of breast cancer (Luminal A, Luminal B, HER2-enriched, basal-like type) can be defined at the gene expression level which also differ in their clinical behavior.^{20–22} For instance, HER-2 positive and basal-like

breast cancer subtypes show the highest five-years LR recurrence rates after BCS plus WBI (7.7–34.0% and 7.1–44.0% respectively).²³ In addition, among younger patients with HER-2 positive tumors, the risk of ipsilateral breast tumor recurrence may be twelve times higher than that of patients with luminal A tumors.²⁴ Conversely, T1-2N0 triple-negative breast tumors treated with modified radical mastectomy without radiotherapy seem to have a significant increased risk of LR recurrence compared with those treated with BCS followed by WBI.²⁵ Therefore, mastectomy does not seem to be a solution in patients with locally aggressive tumors, whereas the implementation of more effective ways to deliver radiotherapy or the development of new systemic treatments is warranted.

The short follow up of all studies available suggests caution before the current evidence on PBI can be generalized to all breast cancer patients. Indeed, recurrences elsewhere in the breast after BCS plus WBI are rare during the first 10 years, but their frequency approximates that of true local recurrences by 15 years.²⁶ This suggests that LR outside the index quadrant behave like new primary disease. Gujral et al found that the number of contralateral breast cancers was at least four times higher than the number of definite ipsilateral new primaries (7.9% vs 1.9%) among 1410 breast cancer conservatively treated at follow up of 15 years, suggesting that WBI reduces the rate of ipsilateral new primary tumors.²⁷ The logical consequence of that might be to return to the bad old days of treating both breasts at the time of the diagnosis of a single primary or to move forward by delivering prophylactic radiotherapy to the opposite healthy breast.^{28,29} Surely these “new primaries” enjoy the same prospects of cure as the original and furthermore the women will be on average a decade older and therefore even more likely to die of old age or co-morbidity than breast cancer.

LR control and survival

For many years several randomized controlled trials consolidated the dogma that local control had no influence on overall survival. In fact, at a follow up of 20 years, BCS plus WBI and mastectomy were associated with the same overall survival in spite of a small but significant advantage in terms of local control for mastectomy.^{2,3} Furthermore, the B-04 randomized trial by the National Surgical Adjuvant Breast and Bowel Project (NSABP) comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation, after a median follow up of 25 years failed to show a significant survival advantage from removing occult positive nodes at the time of initial surgery or from radiation therapy to the axilla. This happened despite a higher LR recurrence rates in women who received no axillary treatment as compared to the other two groups ($P = 0.002$ for the three-way comparison).³⁰ All of these trials suggest that less extensive local treatments may slightly increase the rate of LR recurrence, but have no influence on long-term overall survival.

On the contrary, the 2005 overview released by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that the avoidance of a local recurrence in the conserved breast after BCS could actually influence breast cancer mortality. In particular, it was demonstrated that differences in local treatment that substantially affect local recurrence rates would avoid about one breast cancer death over the next 15 years for every four local recurrences avoided.³¹ A subsequent meta-analysis from the EBCTCG confirmed that radiotherapy after breast conserving surgery halves the recurrence rates and reduces the 15-year risk of breast cancer death from 25.2% to 21.4% (absolute reduction 3.8%, $2p = 0.00005$).³²

The apparently conflicting results obtained from single randomized trials versus large overviews may be reconciled considering that very large numbers are needed to detect survival

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