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Locoregional Therapy for the Primary Tumour in Women with a De Novo Diagnosis of Metastatic Breast Cancer

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Abstract

Purpose of Review The role of locoregional treatment (LRT) in the setting of metastatic breast cancer (MBC) is widely debated due to conflicting results on the impact on outcomes. This review provides a brief overview and evaluation of current evidence.

Recent Findings The majority of retrospective studies suggest LRT provides some survival benefit, but it is not known exactly which subgroup of patients would benefit the most. The significant concerns about inherent biases associated with these studies make interpretation of results challenging. Recent data from prospective clinical trials are conflicting and suggest that adding LRT to treatment regimens makes no difference to health-related quality of life.

Summary Based on the limited high-quality evidence, there is uncertainty that LRT improves outcomes in patients with MBC, and it should not become standard clinical practice. Further prospective research focused on whether subsets of patients benefit from LRT is required.

Keywords Locoregional therapy · Metastatic breast cancer · Breast surgery

Introduction

Breast cancer is the most common cancer amongst women in the United Kingdom (UK) [1]. According to the Global Burden of Disease Cancer Collaboration, in 2017 an estimated 1.9 million women were newly diagnosed with breast cancer, with approximately 601,000 deaths amongst women from breast cancer, making it the principal cause of cancer-related death in women [2].

Owing to the development of national screening programmes and improvements in imaging techniques, most patients are diagnosed with early invasive breast cancer. Globally, between 5 and 10% of women will have metastatic breast cancer (MBC) at the time of presentation, although there is some variation between countries [3, 4]. Current UK estimates are that approximately 5–7% of women are diagnosed with metastatic spread of breast cancer at presentation, and there are several factors (at both the patient and healthcare level) which influence breast cancer being diagnosed at an advanced stage [5–7].

Improvements in survival for women with de novo stage IV breast cancer have been made in recent decades [8], which have been mainly attributable to improvements in systemic therapy [8], use of therapies directed at HER2 (human epidermal growth factor receptor 2) overexpression [9], or lower disease burden at presentation owing to the ability of modern imaging to identify small volume metastatic deposits. Despite these improvements, current 5-year survival estimates for women with MBC remain low, at 26.2% for patients diagnosed in the UK [10] and 28.1% for women in the USA [11].

As MBC remains an incurable yet heterogeneous condition, treatment objectives focus on control of disease, symptom relief, quality of life and extending overall survival. The mainstay of treatment options include chemotherapy,

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radiotherapy, biological and hormone therapy [12]. Unlike early breast cancer, locoregional treatment (LRT) in the form of surgery to the primary tumour with or without radiotherapy is not standard clinical practice for women with MBC, and has been reserved for palliation of local symptoms such as tumour ulceration. Nevertheless, with evidence demonstrating that removal of the primary tumour in other solid metastatic cancers (such as metastatic renal cell carcinoma [13] and colorectal cancer [14]) may improve overall survival, interest has rapidly expanded over recent decades to apply the same question to MBC—does locoregional therapy improve survival, and should it be performed in the setting of MBC? As survival rates amongst women with MBC gradually increase, the role of LRT within a multimodal approach is gaining traction. However, as published studies present conflicting results and there is wide variation in practice, the use of LRT remains a controversial topic. This article therefore aims to explore and discuss key prospective and retrospective evidence on the efficacy of LRT for women with MBC.

Primary Surgery to the Breast and Axilla in the Setting of Stage IV Breast Cancer

Recommendations on Locoregional Treatment in International Guidelines

Clinical practice guidelines are developed to assist healthcare professionals with decisions about screening, prevention or treatment of a specific condition or disease [15]. The variation in rates of LRT recorded by retrospective studies could reflect differences in recommendations stated by clinical practice guidelines. However, in comparing a selection of guidelines on advanced breast cancer, recommendations for LRT in the setting of MBC are relatively consistent. Guidelines from the National Comprehensive Cancer Network (NCCN) [16], the European Society for Medical Oncology (ESMO) [17] and the German Gynaecological Oncology Group (AGO) [18] are quite consistent in their advice on patient selection for surgery. They state that decision-making should focus on patient preferences, be performed in an individualised manner, yet they also highlight the lack of concrete evidence of LRT to improve OS. Whilst UK guidelines from the National Institute for Health and Care Excellence (NICE) [19] offer recommendations in the context of uncontrolled local symptoms, they do not provide guidance as to the application of LRT in MBC in the same level of detail.

Evidence on Outcomes from Population-Based Cohort Studies

In recent decades, there were numerous retrospective population-based studies which examined the impact of LRT on oncological outcomes for women with MBC [20–27, 28•, 29–35, 36•, 37–43]. The majority demonstrated that the receipt of LRT improved overall survival for MBC patients. A few papers found no survival gain is achieved with the addition of LRT [23, 26]. Reported factors associated with improved survival amongst women undergoing primary tumour resection include younger age [30, 35], fewer metastatic sites [44•], metastases limited to bone [44•] and negative resection margins [20, 27, 43].

However, commentators have recommended appropriate caution in interpreting these findings, due to several factors. First, a large degree of heterogeneity exists in the methodology of the studies, making comparison a difficult task [45••, 46]. Second, there are two important and recognised sources of bias, inherent to retrospective data. These include the upstaging of patients to stage IV after primary surgery (known as stage migration), and selection bias, where patients who have better prognostic features (such as lower tumour/nodal stage, fewer sites of metastasis) are chosen for LRT [47]. Several authors have attempted to partially control for this with statistical methods [20, 28•]. This includes a case-matched analysis from Cady et al., which demonstrated strong evidence for selection bias in women undergoing LRT with MBC, as case-matching eliminated or reduced the apparent survival benefit with surgery [25].

Trends in the Use of LRT Over Time

Two recent papers from the USA, which used data from national cancer databases, have revealed a decline in the use of surgery in MBC over time [28•, 36•]. Using data from the Surveillance, Epidemiology, and End Results (SEER) database, Thomas et al. reported 67.8% of women with MBC receiving surgery in 1988, reducing to 25.1% in 2011. In the largest population-based study of LRT in MBC, Lane et al. observed a smaller decrease in rates of surgery, from 43.1% in 2003 to 41.9% in 2011. These reduced rates over time could be attributed to the availability of a wider number of novel systemic therapies, as well as a more prevalent view amongst clinicians that LRT does not provide survival benefit [36•].

Post-LRT Related Morbidity

It is essential to understand the peri-operative morbidity associated with surgery in the setting of MBC, to be able to engage in informed decision-making consent processes with patients. If surgery is performed as the initial treatment, patients who develop post-operative complications can experience delays to the start of systemic therapy, which could compromise psychological and oncological outcomes.

In a retrospective analysis of the American College of Surgeons National Surgical Quality Improvement Programme (ACS-NSQIP) database, the odds of patients with

MBC experiencing 30-day morbidity was 1.6 times greater, when compared with women who had non-metastatic breast cancer [48]. Similarly, in 2018, Fairweather used SEER data to review rates of locoregional morbidity, such as bleeding, infection or cancer-related pain, in patients with MBC who underwent LRT compared with those who had no LRT. They observed that 'baseline' rates of local tumour symptoms were similar amongst those who received LRT versus those who did not (7.9% vs 6.7%). Amongst women who received LRT, the rates of morbidity recorded after treatment significantly increased to 22.6%, when compared with the pre-operative rate of 7.9%. Their results also demonstrated that, for those patients who had recorded pre-operative local disease symptoms and who underwent LRT, rates of overall post-treatment symptoms were reduced (pre-LRT 100% vs post-LRT 54.5%). However, rates of post-treatment locoregional symptoms amongst women with no initial local disease symptoms but who received LRT were higher when compared with the baseline symptom rates of women who did not receive LRT [49]. These results, whilst not able to confirm causal effects, provide useful evidence when discussing with patients if LRT is a suitable management option, in order to relieve local symptoms.

Evidence from Prospective Studies and Randomised Controlled Trials

With results from population-based data providing only an association between LRT and improved outcomes, there was a need for prospective studies to validate or refute the findings from retrospective studies. This led to a US collaborative multicentre prospective registry across 14 sites, between 2009 and 2012 [50, 51], with results presented at the 2016 American Society of Clinical Oncology annual meeting. Women were observed across two cohorts—cohort A (n = 112) included women with MBC at presentation, and cohort B included those who had metastatic disease diagnosed within 3 months of surgery to the primary tumour (n = 15). The primary outcome was 3-year overall survival. After receiving systemic therapy, patients were then categorised according to their overall response. In cohort A, only patients with partial, complete or stable distant disease were subsequently referred to discuss elective surgery. For women who had a beneficial response to systemic therapy, 39 (41%) received surgery, and the results showed no difference in 3-year overall survival rates between those who had surgical therapy (77%), versus those who did not (76%).

Several randomised controlled trials (RCTs) have studied the effect of LRT on overall survival for women with MBC (Table 1). Three RCTs are complete, and two were terminated prematurely due to low accrual rates. Of the two studies that terminated early [52••, 53], the authors of the Austrian POSYTIVE trial published their results in 2019. Whilst it was underpowered, the results showed a trend in favour of improved overall survival for women receiving systemic therapy without LRT; median overall survival was 34.6 months in the LRT group versus 54.8 months for women receiving systemic therapy alone [52••].

The first RCT was conducted in India between 2005 and 2013. Badwe et al. randomised 173 patients to receive LRT and pre-operative systemic therapy, versus 177 patients to receive systemic therapy alone [54••]. Their results demonstrated no difference in overall survival between the two groups, with median survival in the LRT group of 19.2 months compared with 20.5 months in the no LRT group (adjusted HR 1.05, 95% CI 0.81–1.36). Women in the LRT group did have significantly better local progression-free survival (PFS) when compared with the no LRT group, but this did not translate to an improvement in distant PFS (LRT vs no LRT; median 11.3 months vs 19.8 months). In their discussion, the authors noted results of some laboratory studies, which have shown that progression of distant metastasis can occur after removal of the primary tumour, in congruence with their findings. When reviewing the results of this study, it is important to consider several factors. First, the median overall survival of both groups was lower than estimates for more developed countries [55], possibly owing to more advanced disease stage at presentation of women in India. Second, of the 107 patients with HER2-positive cancer, 92% did not receive anti-HER2 therapy, which was recommended practice in higher income countries at that time. Finally, amongst women in the no LRT group, a small number (n = 18/177, 10%) required palliative surgery to control local symptoms. This indicates that a blanket approach to perform LRT in all patients with MBC is unwarranted, owing to the fact that such a small proportion developed symptoms requiring surgical intervention.

In contrast to these results, a trial conducted by Soran et al. in Turkey found a statistically significant difference in improved overall survival for women receiving LRT [56••]. This was demonstrated at the 5-year mark (LRT vs no LRT; 41.6% vs 24.4%), but interestingly results after 3 years of follow-up showed no real difference in overall survival. The study recruited 274 women to receive initial LRT plus systemic therapy (n = 138) versus systemic therapy alone (n = 136). Similar to Badwe et al., the Turkish trial showed significantly lower rates of locoregional progression in the LRT group (1%) compared with the no LRT group (11%). Subgroup analysis (unplanned) demonstrated improved overall survival was associated with ER (estrogen receptor) positive status, HER2 negative status, age less than 55 years, and with bone-only metastasis, for women in the LRT group compared with the no LRT group.

Khan and colleagues of the Eastern Cooperative Oncology Group in the USA conducted the most recent phase III clinical trial (E2108), and published their initial results in abstract

Table 1 A list of randomised controlled trials, comparing LRT with systemic treatment for women with metastatic breast cancer

Study 1st author and trial location	Enrolment period	Status	Trial arms	Number of patients	Follow-up (median)	OS	PFS
Badwe (India)	2005–2013	Completed	All patients with unresectable tumours who were eligible received CT, responders were included. Patients with resectable hormone sensitive tumours were randomised upfront. Patients were randomised to receive LRT (BCS/Mx and ALND; post-operative RT where indicated.) vs no LRT	Total = 350 LRT = 173 No LRT = 177	23 months	Median OS: LRT = 19.2 months No LRT = 20.5 months	Local PFS - LRT = median not reached No LRT = 18.2 months Distant PFS - LRT = 11.3 months No LRT = 19.8 months
Fitzal (Austria)	2011–2015	Terminated due to low accrual	LRT (BCS/Mx and SLNB/ALND; post-operative RT at investigators discretion) + systemic therapy vs systemic therapy alone	Total = 90 LRT = 45 No LRT = 45	38 months	Median OS: LRT = 34.6 months No LRT = 54.8 months	Local progression rate - LRT = 8.9% No LRT = 17.8% Distant PFS - LRT = 13.9 months No LRT = 29 months
Khan (USA)	2011–2015	Active, not recruiting	Upfront systemic therapy, responders randomised to LRT + systemic therapy vs systemic therapy alone	Total = 256 LRT = 125 No LRT = 131	59 months	3-year OS rate: LRT = 68.4% No LRT = 67.9%	Local progression/recurrence rate at 3 years: LRT = 10.2% No LRT = 25.6%
Ruiterkamp (The Netherlands)	2012–	Terminated due to low accrual	LRT + systemic therapy vs systemic therapy alone	Total = 10	-	-	-
Soran (Turkey)	2007–2012	Completed	LRT (BCS/Mx and SLNB/ALND; post-BCS RT, other RT given at discretion of institution) + systemic therapy vs systemic therapy alone	Total = 274 LRT = 138No LRT = 136	40 months	3-year OS rate: LRT = 60% No LRT = 51%	Overall local progression rate - LRT = 1% No LRT = 11%

ALND, axillary lymph node dissection; *BCS*, breast-conserving surgery; *CT*, chemotherapy; *LRT*, locoregional treatment; *Mx*, mastectomy; *OS*, overall survival; *PFS*, progression-free survival; *RT*, radiotherapy; *SLNB*, sentinel lymph node biopsy; *ST*, systemic therapy; *USA*, United States of America

Table 2 A selection of current clinical trials in progress, investigating the effect of LRT on outcomes in women with MBC

Study ID	Status	Trial location	Study cohort*	Trial arms/groups	Estimated enrolment	Outcome measures	Estimated study completion date
NCT04199520	Not yet recruiting	China	Women with MBC	Patients randomised to surgery with systemic therapy vs systemic therapy only	155 participants	Primary: OS Secondary: PFS, BCSS	2023
NCT03870919	Recruiting	France	Women with ER-positive, HER2-negative newly diagnosed MBC	Single group assignment. All patients to receive palbociclib and letrozole, followed by LRT	200 participants	Primary: OS Secondary: clinical and pathological tumour response, mastectomy conversion rate, locoregional recurrence, PFS, adverse events, quality of life	2026
UMIN000005586	No longer recruiting	Japan	Women with newly diagnosed MBC	All patients receive upfront systemic therapy. Patients randomised to receive primary tumour surgery with further systemic therapy, or systemic therapy alone	410 participants (307 patients randomised at January 2017 [69])	Primary: OS Secondary: local PFS, proportion of patients without metastatic tumour progression, proportion of patients with local symptoms, adverse events after systemic therapy, operative morbidity	2025

BCSS, breast cancer–specific survival; *ER*, estrogen receptor; *HER2*, human epidermal growth factor receptor 2; *LRT*, locoregional treatment; *MBC*, metastatic breast cancer; *OS*, overall survival; *PFS*, progression-free survival

*Abbreviated description of study cohort. For full inclusion criteria, see appropriate study protocol

form in 2020 [57••]. This enrolled 390 patients between 2011 and 2015, randomly allocating 256 eligible women to systemic therapy (n = 131) or primary systemic therapy plus LRT (n = 125). There was no difference between the two groups in rates of overall survival at 3 years, with recorded rates of 67.9% for participants in the systemic therapy only group, compared with 68.4% of the systemic therapy plus LRT group. In addition, there was no statistically significant difference in rates of progression-free survival between the two arms, but 3-year rates of local recurrence or progression were markedly higher in the group who did not receive LRT (systemic therapy only 25.6% vs systemic therapy + LRT 10.2%). These results led Khan and colleagues to conclude that the use of LRT in the setting of MBC does not confer survival benefit.

Meta-analyses of Retrospective and Prospective Data

Several meta-analyses have reviewed the published studies, in an effort to collate all the available evidence [44•, 45••, 58–60, 61•]. Pooled rates of LRT from retrospective studies confirmed that women receiving LRT tended to have smaller primary tumours and a lower metastatic burden [44•, 59, 60]. The largest meta-analysis by Gera et al. in 2020 included 216,066 patients from 42 retrospective and 3 prospective studies across a 17-year period. In two separate analyses of retrospective studies, surgery alone (pooled HR 0.64, 95% CI 0.60–0.68), as well as all LRT (surgery only, surgery with radiotherapy or radiotherapy only; pooled HR 0.68, 95% CI 0.64–0.73), was found to produce a significant reduction in mortality [45••]. Similarly, this positive survival benefit was found in the pooled meta-analysis of three prospective trials (HR 0.81, 95% CI 0.57–1.14) but was not statistically significant. The authors concluded from their analysis of retrospective evidence that patients with ER positive, HER2 positive, bone-only metastasis, a resectable primary tumour, and who had a beneficial response to initial systemic therapy would receive the most survival benefit if receiving LRT.

Despite these optimistic results, the majority of study authors concluded their results should be interpreted with care, citing concerns about the quality and heterogeneity of the available evidence on which their analyses were based.

Patient-Reported Outcomes and Quality of Life (QoL)

Maintaining quality of life for patients with metastatic breast cancer has always been a paradigm of clinical management [12]. QoL research helps to provide an overall evidence-based picture for clinicians to discuss with patients, in joint decision-making processes. It is therefore important to understand if LRT improves quality of life for women with metastatic disease, by reducing or avoiding the symptomatic burden of local

progression. Four RCTs have presented data on health-related QoL [57••, 62–64], although two are only in abstract form, and the results from the ABCSG-28 POSYTIVE trial should be interpreted with caution because of low patient numbers. Nevertheless, LRT did not appear to improve health-related QoL in any study. Coupled with current trial evidence suggesting LRT does not improve overall survival, these results provide evidence against performing LRT in the setting of MBC, except in individual circumstances where local disease symptoms are causing specific psychological or functional harm.

Locoregional Radiotherapy

There is limited high-quality published research looking at what influence locoregional radiotherapy (LRR) has on outcomes, as the majority of evidence is from retrospective reports [65]. Studies reported by Bourgier [66] and Le Scodan [67], and a regional retrospective analysis of data from 18 cancer centres across France by Pons-Tostivint, are available [68]. Bourgier et al. did not observe any significant difference in adjusted overall survival or metastatic progression-free survival between women receiving LRR versus women receiving surgery with/without LRR [66]. In a similar study of 581 patients, Le Scodan et al. assessed the survival impact in women receiving LRT ($n = 320$; LRR only 78%, surgery plus LRR 13%, surgery alone 9%) compared with patients who had no LRT ($n = 261$). However in contrast to the results from Bourgier, multivariate analysis revealed that LRT was associated with improved overall survival (HR 0.70, 95% CI 0.58–0.85) [67]. Pons-Tostivint et al. also found this association in their regional population-based study of 1965 patients, diagnosed between 2008 and 2014 at 18 cancer centres in France. The use of LRR or primary surgery with radiotherapy was associated with reductions in risk of death (LRR HR 0.63, 95% CI 0.49–0.80; surgery with radiotherapy HR 0.61, 95% CI 0.47–0.78), when compared with patients who received no LRT [68].

It is worth noting that, in the Le Scodan and Pons-Tostivint studies, patients who received LRT had more favourable tumour characteristics, with smaller tumours, were less likely to have visceral metastasis and had fewer metastatic sites. This likely indicates a degree of selection bias, which must be taken into account when considering the results [47].

Conclusions

MBC is a heterogeneous condition, and there have been modest improvements in survival over recent decades. The use of LRT in patients with MBC continues to be debated, and its effect on outcomes remains largely unclear due to the limited volume and inconsistent nature of published data from clinical trials. Data from retrospective analysis suggest some women with MBC experience a reduction in mortality with LRT. However, this suggested improvement in survival benefit carries significant caveats in terms of inherent study bias, and clinicians cannot automatically translate these results into clinical practice.

The three completed clinical trials that were developed to investigate if LRT was associated with improved survival have produced conflicting results [54••, 56••, 57••], with no difference to health-related quality of life with LRT.

To summarise, the evidence does not currently support the use of LRT for patients with MBC in routine clinical practice, in order to improve outcomes. It is hoped the results from clinical trials which are underway, will contribute valuable evidence to this difficult subject (Table 2). Future research should focus on identifying if LRT has a survival benefit for a particular subset of MBC patients, as studies which include patients with wide variation in metastatic sites and local disease burden, are unlikely to provide useful information for the future management of individual patients. Clinical trials could also address if the introduction of exclusive LRR conveys any significant benefit, as no trials have been performed in this area.

Abbreviations CI, confidence interval; ER status, estrogen receptor status; HER2 status, human epidermal growth factor receptor 2 status; HR, hazard ratio; LRT, locoregional treatment (e.g. surgery and/or radiotherapy to the primary tumour); LRR, locoregional radiotherapy; MBC, metastatic breast cancer; RCT, randomised controlled trial; SEER, Surveillance, Epidemiology, and End Results database

Declarations

Conflict of Interest Katie Miller, Kieran Horgan and David Dodwell declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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