

Role of Locoregional Treatment in De Novo Stage IV Breast Cancer

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ABSTRACT: It is estimated that approximately 154000 women in the United States have stage IV breast cancer (BC). A subset of this group has metastatic disease at presentation, known as de novo stage IV disease. De novo stage IV BC accounts for approximately 6% of all BC diagnoses in the United States. Traditionally, stage IV BC patients are treated with primary systemic therapy with a palliative intent reserving possible locoregional treatment (LRT) as last resort. There has been a lot of interest in the role of LRT in de novo stage IV BC for the past decade with mixed conclusions. Although this review is not intended to be a comprehensive overview of all literature regarding this topic to date, we will review the recent findings in literature focusing on the studies with larger sample sizes to investigate the role of LRT in de novo stage IV BC.

KEYWORDS: Breast cancer, metastasis, surgery, de novo, systemic treatment

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Introduction

Breast cancer (BC) is the most common cancer in women worldwide.^{1,2} Of patients diagnosed with BC, up to 10% of them have de novo stage IV BC.^{1,3–5} Stage IV BC is considered incurable and systemic therapy has always been the primary mode of treatment.^{2,6} Although stage IV disease is known to have a poor prognosis, the survival rates of patients with de novo stage IV BC have improved over the past few decades.¹ The thought behind improved survival is that there is better understanding of tumor biology and that there have been advances in systemic therapy options.⁶ As it is in early stage BC, the expected survival for patients with stage IV BC is also variable based on respective tumor biology and individual response to systemic treatment.^{6,7} The survival for stage IV BC patients ranges from only a few months to many years, median survival being 18 to 24 months.¹ Based on the SEER data, the 5-year survival rates for patients with stage IV BC is 11% to 42% depending on BC phenotype.¹ Despite improved survival seen in the recent decades, locoregional treatment (LRT) has always been reserved as last resort for a palliative intent, mostly for symptom control with the hopes to improve a patient's quality of life.^{2–5,7}

However, it has been shown that LRT of the primary tumor improves survival in stage IV disease in other cancer settings, as in metastatic melanoma, renal cell carcinoma, colorectal cancer, and gastric cancer.⁶ It is believed that the removal of the primary tumor may have an immunomodulatory effect, decrease the overall tumor burden, and remove a “seed source” for possible new metastases.⁶ For BC specifically, there have been several retrospective studies showing improved survival with surgical treatment, but this has not been consistently re-demonstrated in prospective analysis.⁷ Therefore, current National Clinical Cancer Network (NCCN) guidelines recommend

personalized treatment plans with consideration for surgery in certain subset of patients with de novo stage IV BC.

Retrospective Studies

Several retrospective studies have shown improved survival with locoregional therapy (LRT) in de novo stage IV setting.^{6,7} In this review, we would like to focus on the recent publications specifically those with larger same sizes looking at the role of LRT for de novo stage IV BC (Table 1). A French study by Pons-Tostivint et al⁸ in 2019 describes a 35% survival benefit with LRT, HR = 0.65. This study focuses on the tumor subtype, metastatic sites, and overall disease burden as potential predictors of benefit from LRT. It is important to note that LRT was not associated with better survival in triple-negative BC (TNBC). Also, there was significantly better survival with single-site disease. For those patients with more than 2 metastatic sites, there was no survival benefit initially; however, there was benefit with LRT at a later time in those who continued to have controlled disease with more than 1 year survival. Therefore, it was concluded in this study that the number and sites of metastases should not exclude patients from consideration for LRT as long as there is proof of controlled disease on their respective systemic therapy regimens. A study from Hong Kong by Co et al⁹ in 2019 also aims to review the survival of patients with surgical treatment in stage IV setting and reports 10% survival benefit with LRT, $P = .026$. In this study, advanced age and presence of visceral metastasis were associated with worse survival while estrogen receptor positivity (ER+) was the only positive prognostic factor. Therefore, it was concluded in this study that surgery may be beneficial in stage IV setting in select group of patients, specifically in ER+ group. A meta-analysis of 30 observational studies by Xiao et al¹⁰ in 2018 showed that surgical treatment significantly



Table 1. Retrospective studies and meta-analyses evaluating the benefit of LRT.

AUTHORS	N	SURVIVAL BENEFIT WITH LRT	CHARACTERISTICS	STATISTICAL ANALYSIS
Pons-Tostivint et al ⁸	4276	35%	Better OS: <ul style="list-style-type: none"> • HR(+)/HER2(-) • HER2(+) • Bone only • Visceral metastasis without brain Worse OS: <ul style="list-style-type: none"> • TNBC 	HR=0.65
Co et al ⁹	1769	10%	Better OS: <ul style="list-style-type: none"> • ER(+) Worse OS: <ul style="list-style-type: none"> • Advanced age • Visceral metastasis 	P=.026
Xiao et al ¹⁰	67272	N/A	Better OS: <ul style="list-style-type: none"> • Single site • Bone only • Negative margins Worse OS: <ul style="list-style-type: none"> • Positive margins • Greater than 3 metastatic sites 	HR=0.65
Wong et al ¹¹	483	5 year OS in NED group versus no NED 98% vs 45%	<ul style="list-style-type: none"> • 13% achieved NED • 59% of the NED group had LRT • 79% of the NED group had single-site disease 	NED status HR=0.014
Kommalapati et al ¹²	67978	45 vs 24 months	<ul style="list-style-type: none"> • Prognostic scoring system (score 0-17): 5 year OS by group • Group 1 (score 0-7): 48% • Group 2 (score 8-17): 16% 	P<.0001
Lin et al ¹³	8582	50% reduction in mortality risk in M1a group with LRT	M1 subdivision: <ul style="list-style-type: none"> • M1a: single site except brain or liver • M1b: liver only OR multiple sites except brain or liver • M1c: brain OR liver and other sites except brain 	P<.001
Gera et al ¹⁴	216066	31.8% reduction in mortality	Prognostic factors: <ul style="list-style-type: none"> • Bone disease, HER2+, ER+/PR+, disease burden, performance status 	HR=0.6823
Akay et al ¹⁵	172	50% OS with surgery and RT together	Different from other studies as this was the only study looking at metastatic IBC	P<.0001

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HR, hormone receptor; HER2, HER2-neu receptor; RT, radiation therapy; IBC, inflammatory breast cancer; LRT, locoregional treatment; NED, no evidence of disease; OS, overall survival; TNBC, triple negative breast cancer.

improved overall survival (OS), HR = 0.65. This study reports single-site disease, bone-only disease, and negative margins were associated with better survival. A US study looking at HER2 positive (HER2+) stage IV BC population specifically by Wong et al¹¹ showed that the patients with ER+ disease and those who achieved no evidence of disease (NED) status have a very high progression-free survival (PFS) and OS. This study reports that NED patients more frequently had single-site metastasis (79% vs 51%, $P=.005$) and surgical resection of the tumor (59% vs 22%, $P\leq .001$).

There have been recent efforts to help differentiate which subset of patients benefit from LRT. Kommalapati et al in 2018 describes a prognostic scoring system to predict the prognosis in de novo stage IV BC patients treated with LRT. The study describes a 17-point prognostic scoring system (0-17), with higher scores signifying poorer prognosis.¹² The prognostic scoring system looking at 11 independent prognostic factors

resulted in a significantly different 1-, 3-, and 5-year OS based on the respective scores, $P<.0001$. Although the study observed better OS with LRT overall, LRT was associated with lower OS in the high scoring group. Therefore, the study suggests that LRT may benefit a select group of patients with indolent disease. Going along with the goal to specify which subset of stage IV disease would benefit the most from LRT, Lin et al¹³ in 2019 describes the idea of subdivision of M1 stage to better predict prognosis and response to LRT. It is well-known that patients with de novo stage IV BC express heterogeneity with different clinicopathologic and prognostic factors. The M1 category was subdivided into 3 sub-categories based on sites of disease and disease volume. Involvement of brain or liver and increased number of metastatic sites involved were identified as independent worse prognostic factors. This study showed that patients with the M1a subtype (single site involvement except brain and liver) benefited most from LRT, 50%

reduction in mortality risk. However, this survival benefit was not seen in the other subgroups with higher metastatic disease burden. As seen in other studies, the authors conclude that the treatment plans should be made in a multidisciplinary setting with LRT being strongly considered for select group of patients with favorable prognostic factors. Most recently, Gera et al¹⁴ in 2020 published the largest meta-analysis regarding the question of LRT in de novo stage IV setting. This study showed that LRT resulted in significant 31.8% reduction in mortality, HR=0.6823. Therefore, the study also concludes that LRT should be considered in selected patients with multidisciplinary discussion. It also adds that further research is needed to understand the molecular mechanism behind how primary tumor influences the location, development, and growth of metastatic foci with the hopes to help identify patients who will mostly likely benefit from LRT.

It is interesting to note that the benefit of LRT in metastatic setting was also seen in inflammatory breast cancer (IBC) patients in a study by Akay et al¹⁵ in 2014. This study showed that treatment with surgery plus radiotherapy and response to chemotherapy were significant predictors for better OS and distant progression-free survival (DPFS). Local control was significantly higher in patients who underwent LRT compared with patients who received chemotherapy alone (81% vs 18%, $P < .0001$).

As noted above, the common message on the role of LRT in stage IV BC is that careful patient selection is key in the decision-making process. As stated before, different prognostic factors that would be helpful in the decision-making process regarding LRT include the following: good performance status, tumor biology, disease sites (ie, solitary or oligometastatic disease—commonly defined as distant metastasis limited to 1-4 sites), long disease-free interval, and the feasibility and likelihood of complete resection with negative margins.² It is important to point out that since tumor biology is considered a key prognostic factor with luminal phenotype being more favorable compared with TNBC, a repeat biopsy should be obtained on the metastatic site or sites if possible due to the possibility of heterogeneity of biomarkers between different sites. In addition, the different sites and volume of metastatic disease is extremely important as brain and liver metastases are considered poor prognostic indicators where bone-only disease is considered favorable.

Prospective Studies

Although many retrospective studies over the past decade have shown survival benefit with LRT of the primary site, the results from the few available prospective studies are mixed. Therefore, the impact of LRT in stage IV BC is still inconclusive at this time.

There are three prospective studies with negative conclusions. First, a prospective analysis of surgery and survival in stage IV BC, Translational BC Research Consortium (TBCRC) 013 trial by King et al,¹⁶ reports that the response to

systemic therapy was significantly associated with OS and among responders, LRT did not affect OS irrespective of BC phenotype. In this US-based study with median follow-up of 54 months, it is important to note that it was a small study with only 128 patients included in the analysis; also, 17 (15%) patients with no response to systemic therapy were excluded from the analysis. Of the patients with response to systemic therapy, 39 (43%) patients underwent LRT. Although this study concluded that LRT did not affect OS in the whole cohort, LRT did make a difference in HER2+ subset with the 3-year survival being 100% with LRT versus 75% to 88% without LRT, $P = .07$. Looking at this subset analysis, one may suggest that having a bigger sample size may have shown a statistically significant OS benefit with LRT, especially in the HER2+ subset.

The second study is a randomized trial looking at LRT versus no treatment of primary tumor by Badwe et al,¹⁷ which reports no difference in OS between the two groups, with median follow-up of 23 months. In this Indian study, however, the systemic therapy used in the study was different from the usual standard, for example, only a small subset of the HER2+ patients received targeted HER2 therapy and there was limited use of Taxane-based chemotherapy.

The third study with a negative result is a prospective randomized phase III ABCSG-28 POSYITIVE trial, which was stopped early due to poor recruitment.¹⁸ Overall, 90 patients were included with median follow-up of 37.5 months. The patients were randomly assigned to surgical resection followed by systemic therapy (Arm A) or primary systemic therapy only (Arm B). The study did not show OS benefit with surgical resection (34.6 months vs 54.8 months, HR=0.691), instead the study demonstrates a statistically non-significant trend toward worse PFS and OS in patients undergoing surgery. It should be noted that the study did not reach the intended sample size of 254 patients, which was required to detect a clinically relevant treatment effect; therefore, the results should not be interpreted as conclusive at this time.

On the contrary, a positive study was reported from Turkey, a randomized trial comparing resection of primary tumor with no surgery, Protocol MF07-01 by Soran et al.¹⁹ With median follow-up of 55 months, there was no difference in the 3-year OS; however, statistically significant difference was seen in the 5-year OS with LRT. In this Turkish study, however, stage IV patients were offered surgery upfront which is not routinely done in the United States. In addition, the patients in LRT group had more ER+ BC and less TNBC, which brings up the question of whether the indolent tumor biology may be the actual driving factor affecting OS irrespective of LRT. This group recently presented updated results at the San Antonio BC Symposium in 2019.²⁰ This final analysis showed significant 10-year OS benefit with LRT, 46 months vs 35 months, HR=0.71. This study looked at many prognostic factors including LRT, hormone receptor positivity, disease burden, and sites of metastases. Based on the multivariate analysis, LRT was the only prognostic factor that was associated with

Table 2. Prospective trials evaluating the benefit of LRT.

	COUNTRY	STUDY DESIGN	ACCRUAL PERIOD (STUDY START DATE-PRIMARY COMPLETION DATE-STUDY COMPLETION DATE)	SAMPLE SIZE	ACCRUAL
Analysis of Surgery in Patients Presenting with Stage IV BC	USA (NCT00941759)	Prospective cohort	2009-2020-2020	100	Active
Standard of Care Therapy with or Without Stereotactic Radiosurgery and/or Surgery in Treating Patients with Limited Metastatic BC	USA (NCT02364557)	Randomized Parallel assignment	2014-2022-2027	402	Recruiting
Local Treatment in ER-positive/HER2-negative Oligometastatic BC (CLEAR)	Korea (NCT03750396)	Single group assignment Endocrine and local treatments	2018-2021-2025	110	Recruiting
Locoregional Treatment and Palbociclib in de Novo, Treatment Naive, Stage IV ER+, HER2- BC Patients (PALATINE)	French (NCT03870919)	Single group assignment	2019-2023-2026	200	Recruiting
Compare the Efficacy of Surgery Combined with Systemic Therapy and Pure Systemic Therapy in Patients with Stage IV BC	China (NCT04199520)	Randomized Parallel assignment	2020-2021-2023	155	Not yet recruiting
Early Surgery or Standard Palliative Therapy in Treating Patients with Stage IV BC (ECOG 2108 trial)	USA, Canada (NCT01242800)	A randomized phase III trial	2011-2022-2027	391	Active
The Eligibility of Primary Tumor Resection for De Novo Stage IV BC Patients	Japan (UMIN00005586)	A randomized phase III trial Systemic therapy	2011-2018	600	Active
Bone Metastasis and Breast Surgery; BOMET	Turkey (NCT02125630)	Observational (registry)	2014-2019	460	Active

Abbreviations: BC, breast cancer; ER, estrogen receptor; LRT, locoregional treatment.

better OS, odds ratio (OR)=1.58, $P=.03$. Authors concluded that in de novo stage IV BC setting, those patients who underwent upfront LRT followed by systemic therapy had a 58% higher chance to live at 5 years compared with those who received systemic therapy only.

The second study showing somewhat of a positive result was reported in 2019 by Palma et al. This is a multi-center, randomized, open-label, phase 2 study looking specifically at radiation therapy.²¹ This study compared palliative standard of care treatment alone or stand of care plus stereotactic ablative radiotherapy (SABR) in patients with controlled primary tumor and 1-5 oligometastatic lesions. This study showed that SABR was associated with an improvement in OS (28 months vs 41 months, HR=0.57), but 4.5% of the patients had treatment-related deaths. The study concluded that phase 3 trials are needed to conclusively show an OS benefit and to determine the upper limit of metastatic disease burden where SABR would be beneficial.

Conclusion

It is a known fact that the primary treatment that improves the prognosis of de novo stage IV BC patients is systemic therapy that is effective at controlling the overall disease burden. At

this point in time, there are several retrospective reviews showing survival benefit with LRT in stage IV setting. Some concerns that are raised with the positive retrospective studies are the issues with selection bias. It may be thought that selection bias may be present in that the patients selected for LRT may already have better prognosis from the beginning due to low metastatic disease burden or indolent tumor biology.

There are unanswered questions regarding LRT in stage IV setting: what is the optimal sequence of treatment; which subset of patients should be offered LRT; what if LRT results in delays with starting of systemic therapy due to complications; is there a survival benefit with local intervention to metastatic deposit; and should breast reconstruction and contralateral mastectomy be offered during primary breast surgery. Although more recent data show positive outcomes with LRT overall, the decision to proceed with LRT in de novo stage IV setting deserves multidisciplinary consensus on a case-by-case basis. Since 2013, the results of published randomized clinical trials on this topic are conflicting, but there are more prospective observational studies and randomized controlled trials open worldwide with pending results (Table 2). We remain hopeful for standardized practice guidelines on this topic in the near future.

Author Contributions

Joanna Lee: Literature review, preparing / writing manuscript.

Atilla Soran: Literature review, comments, helping to write and create tables.

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