Oncology
and Radiotherapy©
18(8) 2024: 001-009 • RESEARCH ARTICLE

Local management of metastatic breast cancer will improve the overall survival: A systematic review and meta-analysis study

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ABSTRACT

Background: In women, Breast Cancer (BC) is the most common cancer as well as second cause of death due to cancer. Metastatic Breast Cancer (BC) occurs at diagnosis in about 6% of BC patients and develops in 20%– 50% of patients during their lifetimes.

Method: We performed a systematic review of empirical quantitative studies using the PRISMA statement, the Cochrane guidelines, and instructions for synthesis without meta-analysis in systematic reviews. We performed a systematic review of empirical quantitative studies using the PRISMA statement, the Cochrane guidelines, and instructions for synthesis without meta-analysis in systematic reviews. The analyses were performed using stata software, version 17.

Results: The primary interventions used in the studies were Radiotherapy (RT), Stereotactic Body Radiotherapy (SBRT), Stereotactic Ablative Body Radiotherapy (SABR), and surgery. The duration of OS in studies ranged from 2 years to 5 years. The Overall Survival (OS) rates varied widely, from 45% to 95%, with the highest survival rates observed in studies that utilized SBRT or a combination of SBRT and Intensity-Modulated Radiotherapy (IMRT). The overall pooled effect size OS across all studies was 67.43% (95% CI: 57.68-77.17).

Conclusion: These findings advocate for the integration of surgical approaches in the treatment regimen for breast cancer, suggesting that loco regional therapy may offer substantial survival advantages, while also highlighting the need for careful consideration of the timing and context of such interventions.

Keywords: Breast Cancer (BC), a systematic review and meta-analysis study, metastatic

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Word count: 6148 **Tables:** 02 **Figures:** 02 **References:** 70

Received: 09 July, 2024, Manuscript No. OAR-24-141205
Editor Assigned: 11 July, 2024, Pre-QC No. OAR-24-141205(PQ)
Reviewed: 24 July, 2024, QC No. OAR-24-141205(Q)
Revised: 30 July, 2024, Manuscript No. OAR-24-141205(R)
Published: 07 August, 2024, Invoice No. J-141205

INTRODUCTION

In women, Breast Cancer (BC) is the most common cancer as well as second cause of death due to cancer [1]. Metastatic BC occurs at diagnosis in about 6% of BC patients and develops in 20%-50% of patients during their lifetimes [2]. Patient survival has been improving, indicating improved treatment [3]. A subset of patients with MBC presents limited disease, termed 'Oligometastatic' Breast Cancer (OMBC) [4]. Until 2020, there will be at least 170,000 women in the US with metastatic BC [5].

Approximately 5%-10% of women diagnosed with breast cancer present with stage IV disease and an intact primary tumor. While a small portion of cases, the management of the primary tumor in stage IV remains common due to the disease's prevalence [6]. These tumors vary in biology and disease burden. The appropriate local management of the primary tumor in stage IV breast cancer, which is largely considered incurable, continues to be debated [7].

The concept of the Oligo Metastatic (OM) state, was described by Hellman and Weichsel- Baum, in 1995 as an intermediate stage between localized *vs*. generalized disease, where tumor extension is related to a few metastases, commonly less than five, with one to two affected organs [8, 9]. The ESO-ESMO global consensus instructions for Advanced BC-5 (ABC-5) consider five lesions to define OM disorder, independent of the number of affected organs. In BC, this phase accounts for 1% to 3% of cases, even though the figures do not represent sufficiently [10, 11]. The brain, bone, liver, lung, and Lymph Nodes (LN) are common areas of metastases for Oligo metastatic Breast Cancer (OMBC) [12]. Given the likelihood of limited spread, it is possible to achieve longer survival, and, in 2%-3% of cases, cure, with aggressive metastasis-directed therapy [13-16].The effective therapy to control the metastatic disease is still unclear [7].

Loco regional therapy (surgery, followed by radiotherapy when indicated) is a potentially curative treatment for patients with non-metastatic breast cancer [17, 18]. In this context, where systemic therapy is the primary treatment, the role of loco regional therapy is uncertain unless required for local palliation.

About 15 years ago, the potential for loco regional therapy to aid survival was suggested based on biological and clinical data. Biologically, it appeared that mesenchymal stem cells in the primary tumor promote metastasis, suggesting that resection of the primary tumor might be beneficial [19, 20]. Subsequently, a series of retrospective analyses using breast cancer data generated

the hypothesis that early loco regional therapy for the primary site may improve survival for patients with stage IV breast cancer [21-23].

Recently talking about Cancer Associated Fibroblasts (CAFs) and Fibroblast Activated Proteins (FAPs) confirm the TME as an important case of cancer management [24, 25].

Local therapy, such as Radiotherapy (RT), also seems to be a crucial component in the treatment of oligo metastatic breast cancer [26, 27]. Two recently published randomized controlled Phase-II trials demonstrated that local therapy same time (Radiotherapy and surgery) of metastases in OM patients caused long-term Progression-Free Survival (PFS) and increased Overall Survival (OS) [28, 29].

Previous randomized clinical trials have also reported benefit for primary surgery to the breast in establishing local disease control [30, 31]. Prospectively enrolled registries may also further delineate the role of surgery in metastatic breast cancer [32]. Current guidelines for the management of stage IV breast cancer consider this a systemic disease and generally reserve primary site treatment for palliation of local symptoms [6].

Recent literature has identified subsets of women who may benefit from aggressive local management [33]. A randomized clinical trial from Turkey, with over 20 months of follow-up, suggested significantly improved survival for patients with solitary bone metastases following complete excision of the primary breast tumor and regional nodes [34]. However, this study is limited by small patient numbers and lack of confirmatory biopsy of the metastatic site and also the role of RT in local management. A retrospective study of 300 women found a survival advantage for those undergoing breast surgery with bone-only metastases [35]. Additionally, a large meta-analysis indicated a survival benefit for women with small primary tumors, fewer comorbidities, and lower metastatic burden [36].

Stage IV breast cancer for palliation, DFS and OS is well established [10, 37, 38]. Previous randomized clinical trials have also reported benefits for primary surgery to the breast in establishing local disease treatment [34, 39]. Additionally, at least one retrospective series has suggested that local treatment, established through early resection of the breast tumor, can be associated with improved survival, although bias was a concern and randomized clinical trials to address this question were urged [38].

In this study, the primary management of breast cancer patients with oligo metastases has been investigated.

MATERIAL AND METHODS

Design

We performed a systematic review of empirical quantitative studies using the PRISMA statement, the Cochrane guidelines, and instructions for synthesis without meta-analysis in systematic reviews [40-42].

Literature search

Studies published in English were carefully searched in biological databases (PubMed, Embase, EBSCO, Web of Science, Science Direct, and Cochrane Library) in September 2012– February 2022. The search terms were as follows: (Oligo metastases, treatment, primary management, or breast cancer), (survival, lesion) and (stage).

Inclusion criteria

Studies that investigated primary treatment methods on breast cancer Stage IV patients with oligo metastases in limited areas were included in the study.

Exclusion criteria

- Abstracts, letters and reviews.
- Non-English language papers.
- Studies did not examine oligo metastatic lesions.
- Studies did not report the percentage and number of oligo metastatic lesions by lesion location.
- Studies that worked on other cancers besides breast cancer.
- Studies that did not focus on primary management.

Study selection

Two investigators reviewed the articles independently, including titles and abstracts, and then full texts were read to select potentially eligible studies. Selections were based on the inclusion and exclusion criteria and any disagreement was resolved by consensus.

Data extraction

Two independent reviewers extracted useful data from the selected studies. The following data were extracted: Author, year, number of samples, type of study, oligo metastatic lesion, primary management, and survival.

Search outcome

We detected 650 articles. Duplicate studies (N=220) were excluded. Also, 430 abstracts were screened and 210 abstracts were extracted and reviewed. In addition, 220 full-text articles were detected considering their title and abstract between September 2012 and February 2021. We found 32 relevant published texts, but after reading their full texts, 25 ones were removed because of Reports excluded (n=9), inconsistency with the objectives of the study (n=4), not available full text (n=3), Review article (n=2) and systematic article (n=1). Finally, 13 articles remained (Figure 1).

Quality appraisal and data extraction

To assess the quality of the quantitative papers, the Quality assessment tool was used. The quality of 32 articles was assessed using the STROBE list, and appropriate 13 articles were included (Table 1). The full-text papers were evaluated before data extraction. This tool is the version adjusted based on a tool designed by the effective public health practice project [43].

The following data were extracted from the articles (Table 2). Two authors extracted the data and referred to a third person in case of disagreements.

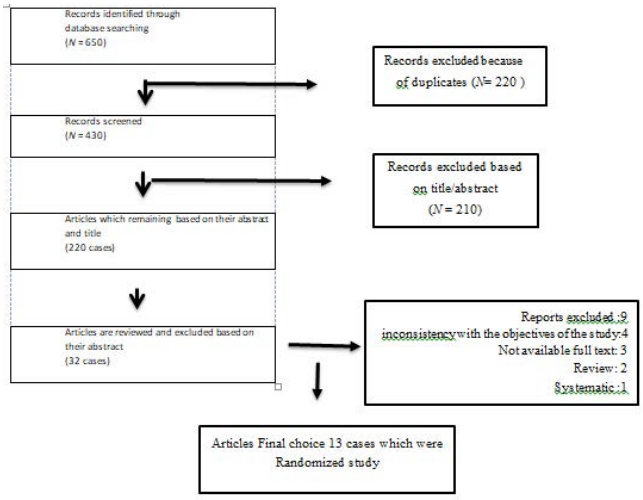

Fig. 1. Flow of information through the various phases of the systematic review

Tab. 1. Strobe Statement—checklist of items that should be included in reports of observational studies

Tittle and Abstracts	1	Indicate the study's design with a commonly used term in the title or the abstract
		Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/Rational	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any pre specified hypotheses
Methods		
Study Design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants
		Cohort study—For matched studies, give matching criteria and number of exposed and unexposed
		Case-control study—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data Sources/Measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study Size	10	Explain how the study size was arrived at
Statistical Methods	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
		Describe all statistical methods, including those used to control for confounding
		Describe any methods used to examine subgroups and interactions
		Explain how missing data were addressed
		Cohort study—If applicable, explain how loss to follow-up was addressed
		Explain how missing data were addressed
		Cohort study—If applicable, explain how loss to follow-up was addressed
		Case-control study—If applicable, explain how matching of cases and controls was addressed
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy
		Describe any sensitivity analyses

Results		
Participants	12	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed
		Give reasons for non-participation at each stage
		Consider use of a flow diagram
	13	Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders
		Indicate number of participants with missing data for each variable of interest
		Cohort study—Summaries follow-up time (e.g., average and total amount)
	14	Cohort study—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main Results	15	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		Report category boundaries when continuous variables were categorized
		If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other Analyses	16	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key Results	17	Summaries key results with reference to study objectives
Limitations	18	Discuss limitations of the study, taking into account sources of potential bias or imprecision
		Discuss both direction and magnitude of any potential bias
Interpretation	19	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalizability	20	Discuss the generalizability (external validity) of the study results
Other Information		
Funding	21	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Statistical analysis

The Cochran Q test and Higgins and Thompson I^2 test were performed to determine the homogeneity between the studies. A subgroup meta-analysis was conducted to examine the effect size of different types of interventions on Overall Survival (OS) outcomes. The random-effects model using the DerSimonian–Laird method was employed to calculate the summary effect size for each group. The results were presented in the form of forest plots with a description of the results in the plots, and the point estimates and their 95% Confidence Intervals (CIs) were calculated accordingly. The regression-based Egger test and Begg's test was performed to evaluate the potential for publication bias. The analyses were performed using Stata software, version 17.

RESULTS

Characteristics of studies

The Table 1 presents the characteristics of 13 studies on the treatment of metastatic breast cancer Stage IV. The studies were conducted in various countries, including the USA, Germany, Korea, Turkey, Italy, China, and Japan. The majority of the studies were retrospective in nature, while one was a prospective study. The studies examined patients with different patterns of metastatic disease, including lung and liver metastases, lung and breast metastases and liver and breast metastases. The sample sizes ranged from 22 patients to 24,015 patients, with the majority of studies including fewer than 100 patients.

The primary interventions used in the studies were Radiotherapy (RT), Stereotactic Body Radiotherapy (SBRT), Stereotactic Ablative Body Radiotherapy (SABR), and surgery. The duration of OS in studies ranged from 2 years to 5 years. The Overall Survival (OS) rates varied widely, from 45% to 95%, with the highest survival rates observed in studies that utilized SBRT or a combination of SBRT and Intensity-Modulated Radiotherapy (IMRT) (Table 2).

Tab. 1. Characteristics of the studies

N	Author and Ref.	Year	Type of Study	Country	OMBC	Sample Size	Intervention	Site	Duration (year)	Overall Survival	Stage 4
1	Lemoine [44]	2021	Retrospective cohort	USA	Lung-liver	47	RT	Lung-liver	3	45	-
2	Weykamp [45]	2020	Retrospective	Germany	Lung-liver	46	SBRT	Breast	3	62.1	-
3	Wijetunga [46]	2020	Retrospective	USA	Lung-breast	56	SABR	Breast	2	67	-
4	Cha [47]	2020	Retrospective	Korea	Liver >2	49	RT/Surgery	Liver	5	89.4	-
5	Onal [48]	2018	Retrospective	Turkey	Liver<5	22	SBRT	Liver	2	57	-
6	Trovo [49]	2018	Prospective	Italy	Liver<5	54	SBRT/IMRT	Liver	2	95	-
7	Xie [50]	2017	Retrospective	China	Breast	223	Surgery	Breast	2	95	-
8	Lane [51]	2017	Retrospective	USA	Breast	24015	Surgery	Breast	4	52	-
9	Scorsetti [52]	2016	Observational	Italy	Liver <4	33	SBRT	Liver	2	66	-
10	Thomas [6]	2016	Retrospective	Chicago	Breast	8330	Surgery	Breast	2	60	-
11	Tan [53]	2016	Retrospective	China	Breast	10441	Surgery	Breast	5	54.1	-
12	Yoo [54]	2015	Retrospective	Korea	Sites <5	50	RT	-	2	85	-
13	Kobayashi [55]	2012	Retrospective	Japan	Lung >5	75	Surgery /RT	Breast	5	79.2	-

Overall survival rate by type of intervention

The analysis included a total of 13 studies, which were categorized into three groups: Radiotherapy (RT), surgery, and both RT and surgery. The RT group, which consisted of 7 studies, had a pooled effect of OS size 68.20% (95% CI: 55.67-80.72). The studies in this group included Yoo (2015), Scorsetti (2016), Trovo (2018), Onal (2018), Weykamp (2020), Wijetunga (2020), and Lemoine (2021). The surgery group, with 5 studies, had a pooled effect of OS size 59.62% (95% CI: 40.76-78.48). The studies in this group were Tan (2016), Thomas (2016), Yoo (2017), Lane (2017), and Xie (2017). The group that received both RT and surgery had a pooled effect of OS size 84.30% (95% CI: 74.30-94.29), based on 2 studies: Kobayashi (2012) and Cha (2020). The overall pooled effect size OS across all studies was 67.43% (95% CI: 57.68-77.17).

The test of group differences revealed a statistically significant difference in the effect sizes between the three intervention groups (Qb=7.00, p=0.03). This suggests that the type of intervention (RT, surgery, or both) has a significant impact on the survival outcomes observed in these studies (Figure 2).

Publication bias

The assessing publication bias using the regression-based Egger test and Begg's test suggests no strong evidence of publication bias in the meta-analysis.

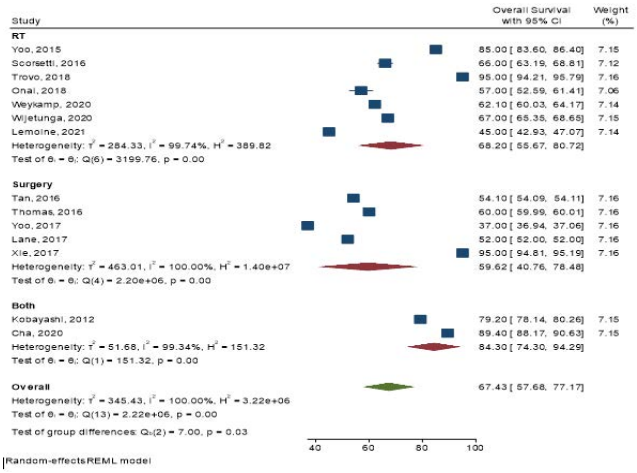

Fig. 2. Overall survival rate by type of intervention

DISCUSSION

Breast cancer is the most prevalent cancer in women worldwide and the main reason why women die from cancer. About 630,000 women lost their lives to breast cancer in 2018, and there were approximately 2.09 million newly diagnosed cases [1, 2].

The concept of the oligo metastatic state was initially described in 1995 as an intermediate stage between loco regional involvement and systemic disease that curatively could be treated if the primary and secondary lesions are addressed. During this stage, metastases are limited in number and usually involve less than five lesions [3, 4]. Although BC has more favorable survival than other cancers, metastatic disease is associated with a significant death rate [5]. For metastatic disease, the primary objective of current treatment approaches is to slow down disease progression and extend survival time, with systemic therapy serving as the foundation of the treatment plan [56]. In a 2015–2016 report by the American Cancer Society, the 5-year and 10-year relative survival rates of BC were respectively 89% and 83% [57]. In a meta-analysis in 2016 performed in the Islamic Republic of Iran, the pooled 1-year, 3-year, 5-year and 10-year survival rates in women with BC were respectively 95%, 80%, 69%, and 55%, whereas the 1-year, 3-year and 5-year survival rates were respectively 91%, 70%, and 59% in a study in Jordan in 2010 [58, 59]. In this systematic review, the reported overall survival rates varied, with pooled 2-year, 3-year, 4-year, and 5-year survival rates ranging from 45% to 95%. The pooled effect size for Overall Survival (OS) across all studies was calculated to be 67.43%.

However, despite the clinical significance of Oligo Metastatic Diseases (OMDs), lack of clinically available biomarkers makes diagnosis challenging [60]. Locoregional therapy (surgery, with accompanying radiotherapy as needed) is effective for nonmetastatic breast cancer. However, 6% or more of new breast cancer cases globally involve concurrent distant metastases [17, 18]. In these instances, systemic therapy is prioritized, making the role of loco regional therapy uncertain unless for local palliation [61].

The role of local treatment with radiation for patients with Stage IV breast cancer remains unclear [62, 63].

Stereotactic Body Radiotherapy (SBRT), which delivers high biologically equivalent radiation doses with pinpoint accuracy to small tumor volumes, has been incorporated as a component of focal therapy in tandem with surgery and radiofrequency radiation [64, 65].

Radiotherapy can decrease the hazard of recurrence by 50%-66% and is measured critical when breast cancer is treated by breast conservative surgery (breast conservation therapy) [36]. In the survey conducted in our study, the survival rate of 68.20% was reported in the researches that used the radiotherapy method for breast cancer patients.

In a 2021 study by Lemoine et al. on 44 oligo metastatic breast cancer patients, systemic treatments and radiation therapy improved survival [44]. Similarly, a 2018 study by Trovo et al. on 54 patients found that radical radiotherapy to all metastatic sites can lead to long-term progression-free survival without detectable toxicity, suggesting it as a valuable treatment option that should be individualized [49]. With the advent of new technologies, breast-conserving surgery (lumpectomy and axillary dissection) in early breast cancers can now be evaluated for its effectiveness over the long disease period and overall outcomes, similar to those of mastectomy [38].

Recent data suggest that Breast-Conserving Surgery (BCS) may positively impact Overall Survival (OS) in early breast cancer [66]. In this review, 5 study only used surgery as Loco regional therapy, the survival rate was reported as 59.62%.

Khan, et al. (2022) founded, 3-year OS was 68.4% with early loco regional therapy in oligo metastatic BC patients [61]. Xie, et al. (2017) study was conducted on 223 breast cancer patients and the results of this study showed Primary breast tumor surgery has a positive effect on the OS of patients with stage IV breast cancer [50]. Zhao et al. study in 2020 was conducted with the aim of local surgery improves the survival of patients with early metastatic breast cancer. The results showed the conclusion that local surgery seems to have a survival advantage that may provide a new understanding of treatment for these patients [67]. The study by Lan et al. in 2017 also used surgical treatment for patients and reported a positive effect on survival [51].

Local therapy is well established as an important palliative intervention for breast cancer patients [68]. However khan's main study results in 2022, support the conclusion that the use of early loco regional therapy for patients with distant metastases at initial presentation does not provide a survival benefit and should not be offered with this expectation [61]. For individuals with distant metastasis who defer early loco regional therapy, about 20% may

eventually require this for local palliation. Although it was associated with improved loco regional control, this had no overall impact on quality of life. However, in this systematic review study, we came to the conclusion that the highest survival rate occurs when two methods of radiotherapy and surgery are used together in the primary management of patients with oligo metastases of breast cancer, and in this study, the survival rate was reported as 84.30%. Two recently published randomized controlled Phase-II trials demonstrated that local therapy same time (Radiotherapy and surgery) of metastases in OM patients caused long-term Progression-Free Survival (PFS) and increased Overall Survival (OS) [50, 67]. Soran et al. in 2021, which was conducted on 278 patients with breast cancer, found local treatment to be more effective than systemic treatment and reported a better effect on patient survival [69]. Lu et al.'s study in 2024, which was performed with the aim of surgery for the primary site of stage IV HER2-positive breast cancer in the evening, considered local treatment (surgery) to be valuable and reported that its use along with systemic treatment is effective on the survival of patients [70]. The study by Cha et al. in 2020, which was conducted on patients with oligo metastatic breast cancer, considered local treatment, which includes surgery and radiotherapy together, to be valuable for the survival of patients [67].

CONCLUSION

In conclusion, recent studies underscore the potential benefits of surgical interventions in improving Overall Survival (OS) for breast cancer patients across various stages. Nobrega (2023) highlighted that Breast-Conserving Surgery (BCS) significantly impacts OS in early breast cancer [66]. Moreover, studies by Xie et al. (2017) and Zhao et al. (2020) revealed that primary tumor surgery and local surgery, respectively, contribute positively to OS in stage IV and early metastatic breast cancer patients [50, 67]. Lan et al. (2017) further supports the efficacy of surgical treatments in enhancing survival rates [51].

However, Khan's main study results in 2022 support the conclusion that the use of early loco regional therapy for patients with distant metastases at initial presentation does not provide a survival benefit and should not be offered with this expectation [61]. For individuals with distant metastasis who defer early loco regional therapy, about 20% may eventually require this for local palliation.

Collectively, these findings advocate for the integration of surgical approaches in the treatment regimen for breast cancer, suggesting that Loco regional therapy may offer substantial survival advantages, while also highlighting the need for careful consideration of the timing and context of such interventions.

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