

MISE AU POINT / IN-DEPTH REVIEW

SURGICAL MANAGEMENT OF PRIMARY TUMORS IN METASTATIC BREAST CANCER

Review of literature

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ABSTRACT • The local control of the primary breast cancer in metastatic patients yields a survival benefit attributed to the reduction of the tumor cell load and activation of the immune system.

Clinical studies do not firmly support this theory and oncologists and oncological surgeons are facing dilemmas in the management of these patients. In this paper, we review the optimal patient profile as well as the type and timing of surgery for primary tumor resection of metastatic breast cancers.

Keywords : breast cancer, resection, surgery, metastasis

INTRODUCTION

Unlike western communities where metastatic breast cancer is a rare occurrence, Middle Eastern countries show a high prevalence of metastatic disease affecting almost 75% of breast cancer cases [1,2]. Metastatic breast cancer had originally been approached as an incurable entity and survival was determined by the evolution of distant metastases rather than by the extent of local disease [3]. However, the benefit of local control in patients with metastatic melanomas and other solid tumors incited this approach in the management of metastatic breast cancer. The biologic rationale resides in decreasing the load of circulating tumor cells and activating the immune system. Further animal studies that evaluated the excision of the primary tumor in metastatic breast cancer are disappointing. Fortunately, the multidisciplinary approach in the clinical setting improved overall survival (OS). Subsequently, surgical excision of the primary tumor in patients with metastatic breast cancer surpassed its common palliative indication to a possible increase in OS [4].

We review in this article, the optimal patient profile and timing of primary tumor resection in patients with metastatic breast cancer. We also discuss the optimal type of surgery to be performed, partial versus complete resection, and lymph node dissection.

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El Rassy E, Atallah D, Chalhoub E, Chelala L, El Kary N, Chahine G, Finan R. La prise en charge chirurgicale du primitif dans le cancer du sein métastatique. *J Med Liban* 2017; 65 (2): 101-105.

RÉSUMÉ • La résection d'un cancer du sein métastatique repose sur le principe de réduction de la charge tumorale circulante et l'activation du système immunitaire. Les études cliniques n'ont cependant pas démontré une amélioration de la survie globale ou de la survie sans progression. Oncologues et oncochirurgiens se trouvent donc souvent devant un dilemme concernant la prise en charge de telles patientes. C'est dans cet esprit que ce travail réexamine le profil et le temps optimal des patientes candidates à une chirurgie. Sont également discutés le type de chirurgie et l'indication du curage ganglionnaire pour aboutir à une prise en charge optimale de ces patientes.

Mots-clés : cancer du sein, résection, chirurgie, métastase

SEARCH STRATEGY AND SELECTION CRITERIA

We conducted an electronic search of the literature published until November 2014 in PubMed and Cochrane Collaboration Database to identify trials studying the resections of primary breast tumors in metastatic disease. The search strategy included the keywords and Boolean operators described as follows: 'breast cancer', 'metastasis' and 'resection'. The language of publication of eligible studies was restricted to English without data limitations. This search was augmented by a hand-search of the reference lists of relevant articles included in the literature review. Two different investigators performed the search and abstracts were independently reviewed. The articles were first selected individually on the basis of their titles by one of the authors. Then, the abstracts of the available articles were examined.

SURGICAL APPROACH TO PRIMARY TUMOR RESECTION

Palliative breast cancer surgery for primary tumor control approaches 15% in patients with primary and secondary metastatic disease [5]. However, the available data shows that the resection of the primary tumor surpasses the palliative approach as it decreases local progression of the primary tumor and increases OS (Table I).

Timing of surgery

To our knowledge only two studies analyzed the optimal timing for surgery [18-19].

The resection of the primary tumor in patients with

TABLE I RETROSPECTIVE STUDIES OF LOCAL THERAPY IN PATIENTS WITH METASTATIC BREAST CANCER.

Study	Period	Number of patients		Overall survival		p value	Hazard ratio (CI 95%)
		Total	Receiving LRT (%)	With LRT	Without LRT		
Khan <i>et al.</i> 2002 [6]	1990-1993	16023	9162 (57)	27.7-31.8% (3 years)	17.3% (3 years)	< 0.0001	0.6 (0.58-0.65)
Rapiti <i>et al.</i> 2006 [7]	1977-1996	300	127 (42)	27% (5 years)	12% (5 years)	0.0002	0.6 (0.4-1.0)
Babiera <i>et al.</i> 2006 [8]	1997-2002	224	82 (37)	95% (3 years)	79% (3 years)	0.091	0.5 (0.21-1.19)
Fields <i>et al.</i> 2007 [9]	1996-2005	409	187 (46)	26.8 months (median)	12.6 months (median)	< 0.0001	0.53 (0.42-0.67)
Gnerlich <i>et al.</i> 2007 [10]	1988-2003	9734	4578 (47)	36 months (median)	21 months (median)	< 0.001	0.63 (0.60-0.66)
Blanchard <i>et al.</i> 2008 [11]	1973-1991	395	242 (61)	27.1 months (median)	16.8 months (median)	< 0.0001	0.61 (0.49-0.76)
Cady <i>et al.</i> 2008 [12]	1970-2002	622	234 (38)	44% (3 years)	24% (3 years)	< 0.0001	N/D
Bafford <i>et al.</i> 2008 [13]	1998-2005	147	64 (41)	4.1 years (median)	2.4 years (median)	0.003	0.47
Hazard <i>et al.</i> 2008 [14]	1995-2005	111	47 (42)	43% (3 years)	37% (3 years)	ND	0.8 (0.4-1.6)
McGuire <i>et al.</i> 2009 [15]	1990-2007	566	154 (27)	33% (5 years)	20% (5 years)	0.0015	N/D
Ruiterkamp <i>et al.</i> 2009 [1]	1993-2004	728	288 (40)	24.5% (5 years)	13.1% (5 years)	< 0.0001	0.62 (0.51-0.76)
Shien <i>et al.</i> 2009 [16]	1962-2007	344	160 (47)	27 months (median)	22 months (median)	0.049	N/D
Leung <i>et al.</i> 2010 [17]	1990-2000	157	52 (33)	25 months (median)	22 months (median)	0.06	N/D
Pérez-Fidalgo <i>et al.</i> 2011 [18]	1982-2005	208	123 (59)	40.4 months (median)	24.3 months (median)	< 0.001	0.52 (0.35-0.77)

CI: confidence interval LRT: locoregional therapy N/D: not determined

breast cancer increases OS significantly when complete staging is performed either before or after surgery. Such issues may arise whenever small tumors without clinical nodal invasion escape routine metastatic exploration. It is essential to note the possible occurrence of the Will Rogers phenomenon when approaching such survival analysis because moving an unrecognized metastatic patient from local to metastatic stage increases the average survival of both stages [18]. In the adequately staged patients, the only benefit is limited to progression free survival and is associated to the resection of the primary tumor at 3-8.9 months after diagnosis [19].

Patient profile

The profile of patients with metastatic breast cancer that would benefit from primary tumor extirpation is yet to be determined (Table II). Published literature demonstrates that local control increases OS in patients with young age, lower stages (tumors < 5 cm), favorable biomolecular profiles (negative HER2), unique metastasis and bone metastasis [7-10]. However, a matched-pair analysis eliminated the apparent survival benefit associated with surgery and proved the selection bias of the earlier reports [12].

In the Pérez-Fidalgo *et al.* study, the surgery group presented more favorable characteristics with better performance status, lesser metastatic sites and visceral localizations. Univariate analysis associated a better OS to the presence of estrogen receptors, the number and sites of metastases, the performance status of the patient and the primary tumor resection. However, surgical resection was retained as the only determinant factor for OS in multivariate analysis [18].

It is noteworthy that the positive outcome obtained with surgery is maintained when the decision to operate is independent from the number of metastatic localizations [23].

Type of surgery

The published series report a 37-61.3% resection of primary tumors in patients with metastatic breast cancer [7-21]. Modified radical mastectomy and lymph node dissection decrease to a greater extent the tumor load and are expected to improve survival especially with the decrease in complication occurrences (Table III) [24]. Historically, Halsted considered that breast cancer disseminates contiguously justifying extensive surgery for better containment of the disease [25]. In contrast, Fisher hypothesized that the spread occurs chaotically throughout blood and lymphatic drainages; consequently, the outcome is unaffected by local control of the disease [26].

The extent of surgical excision was evaluated in the Geneva Cancer Registry Study and the National Cancer Data Base study. In the first study, surgical resection of the primary tumor in patients with metastatic breast cancer increases OS in patients with negative margins whereas patients with positive surgical margins lacked

TABLE II CHARACTERISTICS OF METASTATIC BREAST CANCER PATIENTS RECEIVING LOCAL THERAPY

Study & Recruitment period	Number of patients	Particularities of patients being operated	Factors that prolonged overall survival	Factors that diminished overall survival
Khan <i>et al.</i> 2002 [6] 1990-1993	16023	Not determined	One site metastasis Bone metastasis Negative margins Systemic therapy	Brain metastasis
Rapiti <i>et al.</i> 2002 [7] 1977-1996	300	Young age Lower tumor size & number of involved lymph nodes	Complete excision Total mastectomy	Positive margins (same overall survival as non-operated)
Babiera <i>et al.</i> 2006 [8] 1997-2002	224	Young age Lower tumor burden Liver metastasis HER2 positive	Not determined	Not determined
Gnerlish <i>et al.</i> 2007 [10] 1988-2003	9734	Not determined	Negative margins HER2 negative	Not determined
Fields <i>et al.</i> 2007 [9] 1996-2005	409	Young age Small tumor Fewer bone metastases	Bone metastasis Surgery	Visceral metastasis
Blanchard <i>et al.</i> 2008 [11] 1973-1991	395	Intermediate size tumor Estrogen receptor positive	Hormone receptors positive Lower number of metastases Surgery	Visceral metastasis More than one site of metastases
Cady <i>et al.</i> 2008 [12] 1970-2002	622	Not determined	Neoadjuvant therapy	Not determined
Ruitercamp <i>et al.</i> 2009 [1] 1993-2004	728	More locoregional radiotherapy	Lymph nodes dissection Surgery	Not determined
McGuire <i>et al.</i> 2009 [15] 1990-2007	566	Young age	Surgery	Not determined
Pérez-Fidalgo <i>et al.</i> 2011 [18] 1982-2005	208	Better general condition Less metastatic sites Lower visceral disease	Surgery Total mastectomy Neoadjuvant therapy	Not determined
Dominici <i>et al.</i> 2011 [20] 1997-2007	290	Patients had no prior treatment before surgery	One site metastasis Negative margins Lymphadenectomy if performed 3 months after diagnosis	Not determined
Samiee <i>et al.</i> 2012 [21] 2005-2007	111	Less T4 tumors Less N3 nodes Less visceral metastases	Not determined	Not determined
Parmar <i>et al.</i> 2012 [22] 2005-2013	125	Not determined	HER2 negative Hormone receptors positive	Triple negative

any benefit [16]. Interestingly, patients with positive margins retain a survival benefit in the latter study [6]. In the Pérez-Fidalgo *et al.* study, mastectomy with axillary dissection was performed in 82.9% of patients, while partial or total mastectomy without axillary dissection was undertaken in only 8.9% and conservative therapy in only 8.1% of cases. Overall, the prognosis of patients receiving total mastectomy is better and could be explained by the administration of more cycles of neoadjuvant chemotherapy, the nodal dissections and negative margins. The negative margin status is attributed to the neoadjuvant chemotherapy where patients responsive to neoadjuvant chemotherapy are also more responsive to surgery [18].

TABLE III

DIFFERENT TYPES OF SURGERY USED FOR LOCOREGIONAL THERAPY OF PRIMARY TUMOR IN METASTATIC BREAST CANCER

Study	Total mastectomy	Partial mastectomy
	% of patients	
Khan <i>et al.</i> [6]	62%	38%
Rapiti <i>et al.</i> [7]	69%	31%
Babiera <i>et al.</i> [8]	52%	48%
Fields <i>et al.</i> [9]	55%	45%
Blanchard <i>et al.</i> [11]	78%	22%
Ruitercamp <i>et al.</i> [1]	66%	34%
McGuire <i>et al.</i> [15]	64%	36%

TABLE IV
LYMPH NODE DISSECTION IN PATIENTS WITH METASTATIC BREAST CANCER

Studies	Khan <i>et al.</i> [6]	Fields <i>et al.</i> [9]	Ruitercamp <i>et al.</i> [1]	McGuire <i>et al.</i> [15]
Lymph node dissection (%)	57%	75%	Not calculated	82.9%
Effect of dissection	No benefit due to the small number of axillary dissections	Not determined	Better overall survival but difference restricted to the first year of treatment	Not determined

Axillary lymph node dissection remains controversial although the majority of the published data report the lack of survival benefit (Table IV). However, conclusions cannot be withdrawn from such small sample studies. One possible approach that might confer survival benefit in patients undergoing surgery before complete staging is a mandatory intraoperative sentinel lymph node biopsy. Taffurelli *et al.* demonstrated the effectiveness of this technique in detecting lymph node macroscopic metastasis (metastasis more than 2 mm in size) that allows a sequential proceeding to axillary lymph node dissection during the same surgery.

On the other hand, patients with microscopic metastasis (metastasis between 0.2 mm and 2 mm) or isolated tumor cells (metastasis less than 0.2 mm) on lymph node biopsy did not recur after a 32-month observation [28]. Effectively, the need for lymph node resection in cases of microscopic metastasis is controversial with the minimal detrimental impact [29-31].

LIMITATIONS

Even though most of the published studies demonstrate an increased OS after primary tumor resection in the setting of metastatic disease, a considerable number of authors consider the available studies biased. Bafford *et al.* demonstrated a stage migration bias where the survival advantage in the surgery group faded when taking into account the timing of surgical intervention in patients with pre-surgery staging [13].

Another limitation is the selection bias of retrospective studies where old patients with low performance status, low life expectancy and increased Charlson score are less likely considered for surgery. Moreover, patients selected for surgery are usually not randomized but rather selected by their physicians. In our review, the highest impact of surgery is observed in studies including patients with higher proportion of estrogen-positive cancers, metastatic disease limited to bone localizations, lower number of metastatic localizations, and understaging.

RECOMMENDATIONS AND CONCLUSION

Our exhaustive literature review allows us to retain the following recommendations in Table V.

Biological reasoning allows the assumption that local control of the primary tumor might yield a survival benefit in the setting of distant metastatic breast disease. However, clinical studies failed to confirm this theory.

TABLE V
RECOMMENDATIONS FOR PRIMARY TUMOR RESECTION IN METASTATIC BREAST CANCER

The profile of patients who would benefit from local control
• Younger age
• Lower stages at diagnosis
• Single organ metastasis
• Non-visceral metastasis (only bone metastasis)
• Favorable biomolecular profile: Luminal A (HER2 negative, estrogen and progesterone receptors positive)
• Favorable response to adjuvant or neoadjuvant therapy
The most beneficial type of surgery
• Complete excision with negative margin status
• Total mastectomy
• Lymph node resection preferably 3 months following diagnosis

Unfortunately, trials have been crippled by huge limitations and contradicting results that prevent clear-cut indications. These controversies might be best dealt with by randomized prospective studies. A promising phase III trial conducted by The Eastern Cooperative Oncology Group (ECOG) is planned to evaluate the role of early local therapy for the intact primary tumor in patients with metastatic breast cancer. Its goal is to compare early local therapy to continuation of systemic therapy in patients with stage IV breast cancer whose disease does not progress during initial systemic therapy [32].

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