

THE ROLE OF LOCO-REGIONAL SURGERY IN WOMEN WITH METASTATIC BREAST CANCER AT PRESENTATION

FLORIN-CĂTĂLIN POP¹, LILIANA COLDEA², ALINA FUEREA³, FLORIN GROSU⁴,
CLAUDIA STANCIU POP⁵

¹Department of Surgery, Jules Bordet Institute, Université Libre de Bruxelles, Belgium; ²CFR General Hospital Sibiu, "Lucian Blaga" University of Sibiu, ³Department of Cancer Medicine, Gustave Roussy Cancer Campus, University of Paris-Sud, France; ⁴Academic Emergency County Hospital Sibiu, "Lucian Blaga" University of Sibiu ⁵Department of Pathology, CHU UCL Namur, Université catholique de Louvain, Belgium

Keywords: metastatic breast cancer, surgery, local control, survival

Abstract: Primary metastatic breast cancer (PMBC) is a poor prognosis disease with 5-year overall survival (OS) in 24-39%. The "dogma" of surgery in PMBC was challenged by retrospective studies which suggested that loco-regional surgery (LRS) can improve OS. Clinical advantages are still controversial. The aim of this study is to determine the place of LRS in oncological outcomes of these patients. Relevant PubMed data between 2002-2017 on LRS in PMBC were registered. Twenty-nine publications, 78239 patients were included, 44.4% underwent surgery. Median OS in LRS group was 36.7 months compared to 25.1 month for systemic treatment (ST) group. These findings correspond with those of one randomized trial. The timing and quality-of-life remains uncertainty. LRS may increase OS in PMBC. LRS is reserved for uncontrolled local disease, it should be proposed for women with oligometastatic disease, younger age, indolent PMBC and for responders of ST.

INTRODUCTION

Breast cancer (BC) is by far the most frequently diagnosed cancer among women worldwide and the leading cause of cancer death in women. In 2012, in Romania, nearly 9000 women were diagnosed with BC and 3250 have died from BC.(1) Despite the screening programmes and early detection in the Western countries, 5%-8% of all BC are diagnosed with metastases at presentation, this rate is significantly higher for women in less developed regions.(2,3)

Primary metastatic breast cancer (PMBC) is considered incurable and the goals of treatment are to prolong survival and to ameliorate the quality-of-life (QOL). Systemic (palliative) therapy (ST) is the standard of care but PMBC is a highly heterogeneous disease and there are many factors that influence the therapeutic efficacy: the histological grade, the size of primary tumour (PT), the molecular subtype (MS), the sites and number of metastasis.(4) The therapeutic innovations and new targeted drugs have increased the survival across all BC stages and has led to the concept of stage IV BC as a chronic disease. Actually, the 5-year survival in PMBC is 24-39% with a median survival ranging from 23-32 months.(4,5)

These data, and the relative lack of morbidity of breast surgery (BS), have led to some enthusiasm for the resection of asymptomatic primary breast tumour (PBT), in contrast to the classical "dogma" of surgical treatment reserved for palliation of symptomatic PBT (such as bleeding, ulcerations, pain and/or site infection).(6) Several retrospective studies have focused on the survival benefit of loco-regional surgery (LRS) in PMBC demonstrating that patients with resection of PBT may have longer overall survival (OS).(5) However, the clinical advantages in terms of oncologic outcomes of LRS remain unclear. In other aggressive metastatic cancers like ovarian, renal, colorectal and gastric cancer, an association between decrease in tumour burden and improvement of survival has been shown.(6-8) There are different theories to explain this benefit. It was shown that resection of the PT can remove tumour-induced immunosuppression, stops self-seeding of PT

cells to distant sites, decrease tumour burden, which makes systemic therapy more effective and may remove a source of potentially chemoresistant cell lines.(7-10) In the last two years the new data about LRS in PMBC were published from retrospective studies and especially from prospective studies.(5,9,11-14)

PURPOSE

The aim of this review is to summarize the current literature regarding the place of LRS in PMBC and to determine the impact on LRS in oncological outcomes of these patients

MATERIALS AND METHODS

We performed a selective search on PubMed to identify relevant studies reporting LRS of PT in patients with PMBC from January 2002 to March 2017. The following keywords were used in searching algorithm: "stage IV or metastatic", "breast cancer" and "surgery or primary tumour excision or loco-regional treatment". Studies were included if they reported appropriate survival data for patients with PMBC undergoing surgery or not. In order to assess local control and the different strategies of LRS (conserving or radical surgery, axillary surgery, margins), the additional studies were also included. To analyze each study, we recorded: authors' names, year of publication, source and period of patients data, number of patients in each group and (where available), size of tumour, nodal status, grade of tumour, histology, receptor status, sites and number of metastases and the type of surgery.

RESULTS

A total of 29 studies including 78239 patients met the eligible criteria for our review. Twenty six studies were retrospective, the characteristics are summarized in table no. 1. We find only 3 studies in prospective settings (2 randomized trials and one multicenter prospective registry study), that are reported in table no. 2. Sixteen studies covered the period 1990-2007 (5,6,9,15-27) and 8 were more recent studies with results

²Corresponding author: Liliana Coldea, Str. Constantin Noica, Nr. 20, Sibiu, Romania, E-mail: lilianacoldea@yahoo.com, Phone: +40269 21316
Article received on 23.04.2017 and accepted for publication on 29.05.2017
ACTA MEDICA TRANSILVANICA June 2017;22(2):36-40

CLINICAL ASPECTS

dating from 2000.(8,10-14,28,29) Among the included studies 44.4% of patients (34708) underwent surgery (range 9.8%-83.1%). Data for the type of BS were available in 18 studies (20226 patients): 60.9% of these patients underwent a mastectomy (M), range 40.5% to 100%, and 39.1% were treated with breast-conserving surgery (BCS) range 4.3% to 59.5%.(6,8,12,15-21,25-28,30-33) With regard to the axillary surgery (AS), only 9 studies (750 patients) had the available data.(5,8,15,17,19,26,29,30,33) In this studies, the percentage of AS was 68.5% with ranges from 19%-100%. Concerning the loco-regional progression-free survival (PFS) the data are limited at 6 studies.(8,10,12,13,17,34) Except five of our review studies all other showed an advantage in median OS for patients in LRS group at 36.7 months compared to 25.1 months for those in ST group. The majority of patients undergoing LRS were younger in all studies (except for two).(31,32) In the retrospective studies, patients receiving LRS seem to have less advanced cancer, small number of metastatic sites (1 vs. many) and metastases in bones and soft tissues rather than patients without LRS.

DISCUSSIONS

Overall survival in PMBC

To our knowledge, this is the first review on the role of LRS in patients with metastatic disease at presentation with regard of new mature data from randomized controlled trial. This systematic review confirms a positive impact of LRS in OS of women with PMBC. Surgery of PBT was associated with a statistically significant better OS in 18 of the 29 studies, and a trend for significant better survival in the six remaining studies. The other five remaining studies did not found statistical OS significance difference between the two groups of patients. The median difference in OS between patients who underwent surgery or not was 9.6 months in the retrospective studies. A recent population-based analysis using propensity score methods in 16247 women shows that LRS remained a significant prognostic factor for OS in PMBC patients (HR=0.53, 95%CI=0.50-0.55, $p<0.001$).(3) Several limitations exist about this retrospective studies but these findings seem to correspond to those of one randomized study (MF07-01 trial) which revealed after maturation of data, a statistically significant improvement in median OS with surgery (46 vs. 37 months) at median follow-up of 40 months. The 5-year OS in this trial was 41.6% in the LRS group compared to 24.4% in the ST group (HR=0.66, $p=0.005$).(13) The other two prospective studies failed to demonstrate a significant benefit.(12,14) Many critics have been made to the first randomized trial conducted by TATA Memorial Hospital in India about selection criteria, delays to diagnosis, treatment initiation and planning that could adversely affect survival.(12) More conclusive data about improvement in OS will hopefully come from the publication of other randomized controlled trials (table no. 3).

In the era of personalized medicine, multidisciplinary and targeted treatment approach, the patient selection for LRS is one of the most important criteria which should guide clinicians in the treatment of PMBC. It has been shown, in retrospective studies, that younger age and oligometastatic status can influence the OS of PMBC.(5-8,11,15-17,26,27,29-33) Soran et al. in their randomized trial were able to confirm this, with a higher OS in LRS group than ST group for patients < 55 years (HR=0.57, $p=0.006$), and solitary bone metastasis (HR=0.47, $p=0.04$). The median survival was 14 months higher in the LRS group comparing with the ST group in bone only metastasis (56 vs. 42 months). Another factor that influences the therapeutic efficacy in MBC is tumour biology, and the MS was recently analyzed in a retrospective series by Gong et al. who show that

the MS is an independent prognostic factor and no matter which MS, women who did not have LRS had a worse survival than those who had LRS. The median OS ranged from 13 months for patients with a triple-negative subtype to 44 months for patients with luminal B and human epidermal growth factor receptor 2 positive (HER2+) subtype. Patients with luminal A BC have a median OS at 36 months.(11) In accordance with this, data from MF07-01 trial have confirmed a better OS in LRS group than ST group for hormone receptor (HoR) positive BC (HR=0.64, $p=0.01$).(13)

Type of Surgery

Conservation or Radicality: Few studies have compared the benefit in terms of OS between radical and conservative surgery.(6,19-21,30) Almost two-thirds of patients with LRS underwent a M. Khan et al. in the first retrospective study on surgery in PMBC show a benefit in mean OS for M (32 months) that of BCS (27 months) and the presence of free margins appeared to add incremental independent value.(6) In a large recent retrospective population-based study, Ly et al. show an improvement in OS according to types of local treatment. The median OS was 28 months with M, 23 months with BCS and only 14 months in no LRS ($p<0.0001$).(21) The M appears to be the type of surgery with OS advantages but a BCS is possible for women with PMBC if is optimal.(3,21,30)

Margins. Like in early BC, surgery with free surgical margins brings a larger difference in OS for women with PMBC. Khan and Rapiti found that patients who underwent LRS with complete resection of PT had the longest survival, followed by those with positive margins, while patients who did not undergo LRS had the shortest OS.(6,30) Patients were more likely to have negative margins with M (86%) than with BCS (47%) ($p=0.0083$).(6,17) These patients with negative margins demonstrated a PFS advantage compared with those undergoing surgery with a positive margin ($p=0.03$).(27)

Axillary surgery. The role of AS in loco-regional treatment of women with PMBC is very limited, less than a third of the studies addressed this point. Axillary lymph node dissection (ALND) is with potentially morbidity contrary to BS and was done in 85%-100% of cases. The results are discordant. We noted a trend towards improved survival among the patients who had AS compared with the patients who had not AS in four studies.(26,27,30,33) On the contrary, no impact of ALND on the survival has been demonstrated in the other retrospective studies.(6,8,15,17,23,29) ALND can be proposed in combination with optimal BS in selected patients with initial axillary lymph node (ALN) involvement.(30) A very recent population-based study on 11645 women, performed by Wu et al., analyzed the effect of ALND and ALN status on OS in PMBC. The results showed that ALND improved OS like an independent prognostic factor, the median OS was 38 versus 21 months in the ALND group and non-ALND group ($p<0.001$).(4)

Timing. In most of the retrospective series, the exact timing of surgery is not specified. Generally, LRS is often after ST but the timing of LRS in relation to adjuvant or neo-adjuvant therapies remains an uncertain area in the retrospective studies.(7,15,23) The prospective studies did not show any concrete response about the timing of surgery and ST. The TBCRC 0313 study (14) and TATA Memorial trial (12) failed to show benefice of LRS between responders and non-responders to ST. On the contrary, MF07-01 trial demonstrate an improvement in OS in the group with LRS before ST.(13) In the absence of clear evidence to this specific issue and waiting for a response from ongoing randomized trial, we must consider that primary ST remains the standard approach for PMBC patients before proposing a LRS treatment.

CLINICAL ASPECTS

Table no. 1. Overall survival in patients with PMBC treated with or without loco-regional surgery in retrospective studies

Author	Period	Population Type	Patients	% LRS	Median OS(months/%)		P value	HR
					LRS	No LRS		
Khan 2002 ⁶	1990-1993	NCDB (USA)	16023	57.2	25.3	11.9	0.0137	0.6
Rapiti 2006 ³⁰	1977-1996	Cancer Registry (Geneva)	300	42	27%	12%	0.048	0.6
Fields 2007 ¹⁵	1996-2005	Institutional (Washington)	409	46	26.8	12.6	0.0001	0.53
Gnerlich 2007 ¹⁶	1988-2003	SEER (USA)	9734	47	36	21	0.001	0.63
Blanchard 2008 ³¹	1973-1991	Institutional (Houston)	395	61.3	27.1	16.8	0.006	0.71
Cady 2008 ⁷	1970-2002	Cancer registry (Boston)	622	38	33%	18%	0.0001	NA
Hazard 2008 ¹⁷	1995-2005	Institutional (Chicago)	111	42	26.3	29.2	0.520	0.80
Bafford 2008 ¹⁸	1998-2005	Institutional (Boston)	147	41	42.2	28.3	0.003	0.47
Ruiterkamp 2009 ¹⁹	1993-2004	Cancer Registry (Eindhoven)	728	40	31	14	<0.0001	0.62
Shien 2009 ³²	1962-2007	Institutional (Okayama)	344	47	27	22	0.049	0.89
McGuire 2009 ²⁰	1990-2007	Institutional (Tampa)	566	27	33%	20%	0.0012	NA
Ly 2010 ²¹	1988-2003	SEER (USA)	8761	55.4	BCS 23	14	0.0001	0.73
Leung 2010 ²²	1990-2000	Institutional (Richmond)	157	33	25	13	0.004	NA
Neuman 2010 ⁸	2000-2004	Institutional (New York)	186	37	40	33	0.10	0.71
Ruiterkamp 2011 ²³	1995-2008	Netherlands Cancer Registry	8031	27.4	30.7	16	< 0.001	0.64
Dominici 2011 ²⁴	1997-2007	Institutional (Boston)	551	9.8	42	41	0.27	0.94
BhooPathy 2011 ²⁵	1993-2008	Cancer Registry (Kuala Lumpur)	375	37.1	21.3	10.1	<0.001	0.58
Perez-Fidalgo 2011 ³³	1982-2005	Institutional Valencia	208	59.1	40.4	24.3	0.001	0.52
Shibasaki 2011 ²⁸	2000-2010	Institutional (Sapporo)	92	39.1	25	24.8	0.352	0.70
Rashaan 2012 ²⁶	1989-2009	Institutional (Leiden)	171	35	+	-	0.5	0.9
Samiee 2012 ¹⁰	2005-2007	Institutional (Ottawa)	111	43.2	49	33	0.016	NA
Lang 2013 ²⁷	1997-2002	Institutional (Houston)	208	35.5	56.1	37.2	0.04	0.58
Quinn 2014 ²⁹	2006-2012	Institutional (Galway)	109	47.7	35.8	20.2	0.013	1.09
Thomas 2016 ⁵	1988-2011	SEER (USA)	21372	39.0	28	19	<.001	0.60
Kolben 2016 ⁹	1990-2006	Institutional (Munich)	236	83.1	28.9	23.9	<.001	0.63
Gong 2017 ¹¹	2010-2013	SEER (USA)	7578	37.3	63%	43%	<.001	0.55

Table no. 2 Prospective studies and overall survival for loco-regional surgery or not in patients with PMBC

Study	Period	Population Type	Patients	% LRS	Median OS (months/%)		P value	HR
					LRS	No LRS		
Badwe 2015 ¹²	2005-2013	Randomized Trial (India)	350	49.4	19.2	20.5	0.79	1.04
Soran2016 ¹³	2008-2012	Randomized Trial(Turkey)	274	50.4	46	37	0.005	0.66
King 2016 ¹⁴	2009-2012	Prospective Registry (USA)	90	43.3	71	65	0.85	0.52

Table no. 3. The ongoing Randomized Clinical Trials assessing the impact of LRS in PMBC

Clinical Trials.gov Identifier(Country)	Study period	Size (n)	Initial Therapy	Status
NCT01015625 (Austria)	2010-2019	254	Surgery	Recruiting
NCT01242800 (USA)	2010-2018	880	Systemic therapy	Recruiting
JCOG1017 (Japan)	2011-2016	410	Systemic therapy	Recruiting
NCT01906112(Thailand)	2013-2019	476	Surgery	No record
NCT02125630 (Turkey)	2014–2017	288	Surgery	Recruiting

CLINICAL ASPECTS

Chest wall control and Quality-of-Life considerations

Uncontrolled local disease of BC causes physical and psychological distress, and leads to significant potential for QOL impairment. Therefore, the chest wall control must be another important end point in multimodal treatment of PMBC. Current data are limited to 4 relatively small retrospective series (8,10,17,34) and 2 randomized trials (12,13) summarized in table no. 4. About one third of women in the ST group will present a local progression.(10,17) Moreover, chest wall control was associated in the retrospective studies with improved OS regardless of whether surgical resection of the tumour was performed (HR=0.42).(17) The local control was maintained after surgical resection of the PBT in 82% to 88% of patients (mean follow-up 20-53 months). This finding were confirmed by the 2 randomized trial.(12,13) Badwe et al. showed a significant improvement in loco-regional PFS for patients in LRS group compared with those in ST group (HR=0.16, p<0.0001).(12)

Table no. 4. Association of LRS and local control in PMBC

Study	Patients (%LRS)	Loco-regional PFS		p	Follow-up (months)
		LRS	No LRS		
Carmichael 2003 ³⁴	20(100)	85%	-	NA	20
Hazard 2008 ¹⁷	111(42)	82%	34%	0.002	26.9
Neuman 2010 ⁸	186(37)	88%	-	NA	53
Samiee 2012 ¹⁰	111(43)	86%	56%	0.001	40
Badwe 2015 ¹²	350(49)	99%	90%	0.001	23
Soran 2016 ¹³	274(50)	99%	89%	NA	40

CONCLUSIONS

Although the retrospective data suggest that LRS of the PBT may provide a survival advantage in women with PMBC, this is now confirmed by one of two completed randomized trials. Different hypotheses exist to explain this positive effect, but the true mechanism remains unclear. Therefore, several ongoing promising randomized trials will allow us to better evaluate the role of LRS and will allow us to get solid conclusions regarding the role of LRS, how extensive it should be, its timing, and to better define subgroups of women who should benefit from this strategy in PMBC.

At this time, the role of LRS is reserved for uncontrolled local disease but should be considered and proposed for women with oligometastatic low disease burden, younger age, with a more indolent form of PMBC such as HoR+, and who have responded to initial ST. If surgery is considered, than it should be in accord to optimal oncological outcomes like that in the non-metastatic setting. LRS treatment should be personalized with respect to the clinical and biological heterogeneity of PMBC in order to fulfil individual patient preferences and potentially improve OS with the use of local therapy.

REFERENCES

1. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No.11.[Internet]Available from: <http://globocan.iarc.fr>, accessed on 16/01/2017.
2. DeSantis CE, Fedewa SA, Goding Sauer A, Kramer JL, Smith RA, Jemal A. Breast cancer statistics, 2015: convergence of incidence rates between black and white women. *CA Cancer J Clin.* 2016;66(1):31-42.

3. Warschkow R, Güller U, Tarantino I, Cerny T, Schmied BM, Thuerlimann B, et al. Improved survival after primary tumor surgery in metastatic breast cancer: a propensity adjusted, population-based SEER trend analysis. *Ann Surg.* 2016;263(6):1188-1198.
4. Wu SG, Li FY, Chen Y, Sun JY, Lin HX, Lin Q, et al. Therapeutic role of axillary lymph node dissection in patients with stage IV breast cancer: a population-based analysis.*J Cancer Res ClinOncol.* 2017;143:467-74.
5. Thomas A, Khan SA, Chrischilles EA, Schroeder MC. Initial Surgery and Survival in Stage IV Breast Cancer in the United States 1988-2011. *JAMA Surg.* 2016;151(5):424-31.
6. KhanSA, Stewart AK, Morrow M. Does aggressive local therapy improve survival in metastatic breast cancer? *Surgery.* 2002;132(4):620-7.
7. Cady B, Nathan NR, Michaelson JS, Golshan M, Smith BL. Matched pair analyses of stage IV breast cancer with or without resection of primary breast site. *Ann SurgOncol.* 2008;15(12):3384-95.
8. Neuman HB, Morrogh M, Gonen M, Van Zee KJ, Morrow M, King TA. Stage IV breast cancer in the era of targeted therapy: does surgery of the primary tumor matter? *Cancer.* 2010;116(5):1226-33.
9. Kolben T, Kolben TM, Himsl I, Degenhardt T, Engel J, Wuerstlein R, et al. Local Resection of Primary Tumor in Upfront Stage IV Breast Cancer. *BreastCare.* 2016;11:411-7.
10. Samiee S, Berardi P, Bouganim N, Vandermeer, L, Arnaout A, Dent S, et al. Excision of the primary tumour in patients with metastatic breast cancer: a clinical dilemma. *Current Oncology.* 2012;19(4):270-279.
11. Gong Y, Liu Y-R, Ji P, Hu X, Shao Z-M. Impact of molecular subtypes on metastatic breast cancer patients: a SEER population-based study. *Scientific Reports.* 2017;7:45411.
12. Badwe R, Hawaldar R, Nair N, Kaushik R, Parmar V, Siddique S, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. *Lancet Oncol* 2015;16(13):1380-1388.
13. Soran A, Ozmen V, Ozbas S, Karanlik H, Muslumanoglu M, Ipci A, et al. A randomized controlled trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer: Turkish Study (MF07-01). 2016 ASCO Annual Meeting. Abstract 1005.
14. King TA, Lyman J, Gonen M, Reyes S, Shelley Hwang E-S, Rugo S. H et al: A prospective analysis of surgery and survival in stage IV breast cancer (TBCRC 013). 2016 ASCO Annual Meeting. Abstract 1006.
15. Fields RC, Jeffe DB, Trinkaus K, Zhang Q, Arthur C, Aft R, et al. Surgical resection of the primary tumor is associated with increased long-term survival in patients with stage IV breast cancer after controlling for site of metastasis. *Ann SurgOncol.* 2007;14(12):3345-51.
16. Gnerlich J, Jeffe DB, Deshpande AD, Beers C, Zander C, Margenthaler JA, et al. Surgical removal o the primary tumor increases overall survival in patients with metastatic breast cancer: analysis of the 1988-2003 SEER data. *Ann SurgOncol.* 2007;14(8):2187-94.
17. Hazard HW, Gorla SR, Scholtens D, Kiel K, Gradishar WJ, Khan SA. Surgical resection of the primary tumor, chest wall control, and survival in women with metastatic breast cancer. *Cancer.* 2008;113(8):2011-9.
18. Bafford AC, Burstein HJ, Barkley CR, Smith LB, Stuart Lipsitz S, Iglehart DJ, et al. Breast surgery in stage IV

- breast cancer: impact of staging and patient selection on overall survival. *Breast Cancer Res Treat.* 2009;115(1):7-12.
19. Ruiterkamp J, Ernst MF, van de Poll-Franse LV, Bosscha K, Tjan-Heijnen VC, Voogd AC. Surgical resection of the primary tumour is associated with improved survival in patients with distant metastatic breast cancer at diagnosis. *Eur J Surg Oncol.* 2009;35(11):1146-51.
 20. McGuire KP, Eisen S, Rodriguez A, Meade T, Cox EC, Khakpour N. Factors associated with improved outcome after surgery in metastatic breast cancer patients. *American Journal of Surgery.* 2009;198:511-5.
 21. Ly BH, Vlastos G, Rapiti E, Vinh-Hung V, Nguyen NP. Local-regional radiotherapy and surgery is associated with a significant survival advantage in metastatic breast cancer patients. *Tumori.* 2010;96:947-54.
 22. Leung AM, Vu HN, Nguyen KA, Thacker LR, Bear HD. Effects of surgical excision on survival of patients with stage IV breast cancer. *J Surg Res* 2010;161:83-8.
 23. Ruiterkamp J, ErnstMF, de MunckL, van der Heiden-van der Loo M, Bastiaannet E, van de Poll-Franse LV, et al. *Breast Cancer Res Treat.* 2011;128(2): 495-503.
 24. Dominici L, Najita J, Hughes M, Niland J, Marcom P, Wong YN, et al. Surgery of the primary tumor does not improve survival in stage IV breast cancer. *Breast Cancer Res Treat.* 2011;129(2):459-465.
 25. Bhoo-Pathy NB, Verkooijen HM, Taib NA, Hartman M, Yip CH. Impact of breast surgery on survival in women presenting with metastatic breast cancer. *Br J Surg.* 2011;98:1566-72.
 26. Rashaan ZM, Bastiaannet E, Portielje JE, van de Water W, van der Velde S, Ernst MF, et al. Surgery in metastatic breast cancer: patients with a favourable profile seem to have the most benefit from surgery. *Eur J SurgOncol* 2012;38(1):52-56.
 27. Lang JE, Tereffe W, Mitchell MP, Rao R, Feng L, Meric-Bernstam F et al. Primary Tumor Extirpation in Breast Cancer Patients Who Present with Stage IV Disease is Associated with Improved Survival. *Ann SurgOncol.* 2013;20(6):1893-1899.
 28. Shibasaki S, Jotoku H, Watanabe K, Takahashi M. Does primary tumor resection improve outcomes for patients with incurable advanced breast cancer? *Breast.* 2011;20:543-7.
 29. Quinn EM, Kealy R, O'Meara S,Whelan M, Ennis R, Malone Cet al., Is there a role for locoregional surgery in stage IV breast cancer? *Breast.* 2015;24(1):32-7.
 30. Rapiti E, Verkooijen HM, Vlastos G, Fioretta G, Neyroud-Caspar I, Sappino AP et al. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. *J ClinOncol.* 2006 24:2743-49.
 31. Blanchard DK, Shetty PB, Hilsenbeck SG, et al. Association of surgery with improved survival in stage IV breast cancer patients. *Ann Surg.* 2008;247(5):732-8.
 32. Shien T, Kinoshita T, Shimizu C, Hojo T, Taira N, Doihara H, et al. Primary tumor resection improves the survival of younger patients with metastatic breast cancer. *Oncol Rep.* 2009;21:827-32.
 33. Pérez-Fidalgo JA, Pimentel P, Caballero A, Bermejo B, Barrera JA, Burgues O et al. Removal of primary tumor improves survival in metastatic breast cancer. Does timing of surgery influence outcomes? *Breast.* 2011;20:548-54.
 34. Carmichael AR, Anderson ED, Chetty U, Dixon JM. Does local surgery have a role in the management of stage IV breast cancer? *Eur J Surg Oncol.* 2003;29:17-19.