ISSN: 2474-1353

Junejo et al. Int J Womens Health Wellness 2020, 6:112
DOI: 10.23937/2474-1353/1510112
Volume 6 | Issue 1
Open Access

International Journal of
Women's Health and Wellness

MINI REVIEW

Current Surgical Options for Primary Site in Metastatic Breast Cancer

Kulsoom Junejo[1] FRCS, FACS, FCPS, EBSQ-Breast; Farkhanda J. Dahri[2] FCPS, M. Zafar Chawdhery[3] FRCS(Eng), FRCS(Ed) LLB (Hons)

[1]Asst. Professor of Surgery, Weil Cornell Medical College-Q & Senior Consultant Oncoplastic Breast Surgeon, Surgery Department, Hamad General Hospital, PO Box 3050, Doha, Qatar

[2]Prof. of Surgery, Peoples University of Medical & Health Sciences; and Fairy Medicare Hospital, Nawabshah, Pakistan

[3]Senior Consultant General Surgeon, St Anthony's Hospital, Surrey, UK

***Corresponding author:** *Dr. Kulsoom Junejo, Senior Oncoplastic Breast Surgeon, Surgery Department, Hamad General Hospital, PO Box 3050, Doha, Qatar, Tel: 00974-40257724*

Keywords

Breast Surgery; Stage IV breast cancer; Primary Site; Review

Introduction

Cancer is a major public health problem worldwide that has now become the leading cause of death among adults aged 35-70 years causing twice as many deaths as cardiovascular disease [1,2]. The incidence burden and mortality is closely with sociodemographic indices (SDI) levels and is highest in countries with higher SDI levels [3].

Globally breast cancer remains the commonest type of cancer in women with an estimated 2.4 million new cases diagnosed per year, causing 523,000 deaths in women worldwide [4]. Though its incidence rates vary greatly ranging from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe according to WHO [5]. The global incidence of breast cancer has been rising with annual increases of 3.1%, beginning with 641,000 cases in 1980 and increasing to > 1.6 million in 2010 and this trend is likely to continue [6]. In the United States it effects 1 in 8 women and currently there are more than 3 million women who have been diagnosed with breast cancer [7].

Advances in the imaging modalities has resulted in increased diagnosis of low burden disease and improved systemic therapies have helped to improve survival. Some of the considerations where local control with surgery may be able to provide some meaningful benefit to patients with metastatic breast cancer in the era where significant improvement in systemic treatment options has been achieved are considered here.

A majority (62%) of women at diagnosis in USA have early stage breast cancer where invasive cancer is localized to the breast; and with prevailing effective treatment strategies 5-years relative survival rate is 99% [8]. Nonetheless, an estimated 20-30% of women with early stage breast cancers will go on to develop metastatic disease where as between 6-10% of newly diagnosed women with breast cancer have stage IV disease at presentation [9]. Although some women with stage IV breast cancer may survive for many years it carries a poor prognosis with median survival between 18 to 24 months [10] and 5-year survival of only 27% [11]. It is estimated that about 90% of deaths in breast cancer are caused by distant metastases [12]. Stage IV breast disease is rarely encountered in practice before diagnosis of primary site cancer.

Metastatic breast disease is essentially incurable and conventional mainstay of treatment for stage IV disease has been medical therapy only with varying outcomes and in general primary site surgery as local

Citation: Junejo K, Dahri FJ, Chawdhery MZ (2020) Current Surgical Options for Primary Site in Metastatic Breast Cancer. Int J Womens Health Wellness 6:112. doi.org/10.23937/2474-1353/1510112

Accepted: March 11, 2020: **Published:** March 13, 2020

therapy for asymptomatic patients is not offered routinely due to lack of clear evidence of any beneficial survival advantage. The role of surgery in the treatment of these patients remains controversial and has thus far been limited. It has mainly been palliative in nature and by far and large confined to a select subgroup of patients for helping to improve quality of life e.g. alleviating intractable pain or for those lesions which are large, fungating or ulcerating. It addresses quality rather quantity of life issues.

Currently the decision to offer surgery for the primary site in exceptional circumstances is made on a case-by-case basis in a multidisciplinary setting as it is a heterogeneous disease on the molecular level. It has been argued that surgery may be more useful in patients with human epidermal growth factor receptor 2 (HER2) &/or ER positive disease, who have a rapid and dramatic response to systemic therapy but there is lack of evidence to support this approach. In addition, radiation therapy is not routinely used as in primary curative treatment for non-metastatic disease if lumpectomy of the primary lesion is offered and reconstructive surgery is only limited to closing a large mastectomy wound.

Previously analysis from National Cancer Database in USA [13] and metanalysis of large single-institutional databases, have reported improved survival in some patients with metastatic disease who had surgery for treatment of primary breast tumor and who had earlier received systemic therapy. These data although retrospective had concluded that the surgical resection of the primary breast tumor was independently associated with a statistically significant improvement in overall survival [14-17]. This has been attributed to cytoreduction of tumor burden [18] and/or depletion of mesenchymal stem cells within tumor stroma that promote metastases in breast cancer [19]. But there remains the possibility of selection bias in these studies in that breast surgery may have been offered only to those who had a longer potential for survival in the first place. However, it can reasonably be argued that removing the primary tumor reduces the risk of further metastatic spread or reseeding is eradicated, it decreases the chance of emergence of chemo resistant chemo resistant cells as breast cancer is a heterogeneous disease and under stress cancer stem cells may undergo symmetric self-renewal increasing tumor resistance to systemic therapy. Furthermore, decreasing the tumor bulk may restore immune competence of the host as lower tumor burden in limited stage IV disease makes it potentially more responsive to treatment [20,21]. It has been suggested that in local recurrence, surgery should be the primary treatment of choice whereas that axillary staging can be redone in patients with a previous negative sentinel node biopsy [22].

Interestingly in the Spanish El Álamo registry analysis of 1415 patients with de novo metastatic breast cancer patients diagnosed between 1990 and 2001 primary tumor surgery was associated with better overall survival in the primary site surgery group. This was independent of metastatic location, histological type, histological grade, hormone receptor status and tumor size; suggesting that locoregional therapy of primary tumor should be considered as part of the therapeutic strategy for selected patients with advanced breast disease [23].

In contrast, based on previous randomised trials and existing evidence in 2018 Cochrane Library Database of Systematic Reviews did not come a definitive conclusions on the benefits and risks of breast surgery associated with systemic treatment for women with stage IV disease. It was argued that while primary site breast surgery may improve the control of local disease it probably worsened control at distant sites [24].

Recent prospectively randomised trials, from India, Turkey and Austria did not convincingly demonstrate any useful survival advantage from surgery to the primary site in stage IV breast cancer [25-27]. Therefore, from the available data there does not appears to be overwhelming evidence of benefits of breast surgery with its inherent associated risks, when comparing with systemic treatment alone for patient with metastatic breast cancer. However, the patients in the aforesaid studies were a very heterogeneous group in terms of the number of metastases at baseline, the involved metastatic sites e.g. bone, liver, brain, lungs and so on. Further the issue of the breast cancer subtypes and the systemic treatments for each subtype and then how surgery plays a role in that background had not been addressed either. The relatively poor outcome may be reflection of the dogma that the removal of primary site tumor is not a local phenomenon. Arguably it increases the labelling index in distant metastases because of increase in serum growth factors secondary to immunosuppression [28] and trauma caused by surgery, as was shown in animal models [29,30]. Primary tumor is a source of antiangiogenic factors and growth factors inhibitors, therefore its removal may result in an accelerated distant relapse, suggesting that the intervention could even be disadvantageous [31]. As survival is determined by metastatic burden and not local therapy, the biological rationale for removing the primary in case of proven disease dissemination does become questionable.

Therefore, given the conflicting data available and in keeping with the prevailing ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer [32] the role of surgery of the primary site tumor, at present in general, remains to be determined on a case-by-case basis for selected few patients who show excellent responses to systemic therapy and have a low burden of distant disease [33]. A number of major questions still remain unanswered such as which patients would really benefit the most from surgery and what is appropriate timing of surgery in those patients i.e. whether it should

be undertaken at the outset before any systemic therapy or should it be after initialising systemic therapy. Is systemic therapy first followed by surgery approach is more beneficial or whether there is improved survival compare to those who don't have surgery? It is hoped outcome from trials such as Eastern Cooperative Oncology Group (ECOG) E2108 in the US and the Japanese Cooperative Oncology Group (JCOG) 1017 in Japan may be able to address some of these issues.

Both trials have now completed enrolment. ECOG is a randomization trial of surgery or no surgery in patients who have systemic therapy first and have some response to therapy. The endpoint is to evaluate overall survival and quality of life as well as the incidence of uncontrolled chest wall disease among those undergoing local management of the primary site disease with metastatic breast cancer [33]. JCOG is a prospectively randomised trial of over 400 stage IV patients to confirm the superiority of primary tumor resection plus systemic therapy over systemic therapy alone in patients who are sensitive to primary systemic therapy [34].

In conclusion the important role of surgery in individuals with locally advanced breast cancer to achieve adequate locoregional control will remain palliative in nature for now until the results of current trials in progress are available. In the meantime it is suggested that breast surgery of the primary tumor may be offered to select few patients with de novo metastatic breast cancer after initial response to first-line systemic therapies who have luminal or HER2-positive biology, a good performance status, oligometastatic disease and limited if any visceral involvement. The patients and their clinicians working together would have to try to ascertain which patient is more likely to benefit from the surgery at the primary site in a metastatic breast cancer setting in a shared decision making environment.

Acknowledgements and Funding

No grant and funding was offered nor used for this review.

Author Contributions

Both authors contributed equally in writing the paper and reviewing the literature.

Ethics Approval

Not required for this review.

Competing Interests

The authors declare that they have no competing interests.

References

1. Dagenais GR, Leong DP, Rangarajan S, Lanas F, Lopez-Jaramillo P, et al. (2020) Variations in common diseases, hospital admissions, and deaths in middle-aged adults in 21 countries from five continents (PURE): A prospective cohort study. The Lancet 395: 785-794.
2. Singh A and Siddiqui AM (2019) The Transformation of the Clinic and the Epidemiology of Diseases: The Times they are a Changing. Epidemol Int J 3: 000131.
3. Hu K, Ding P, Wu Y, Tian W, Pan T, et al. (2019) Global patterns and trends in the breast cancer incidence and mortality according to sociodemographic indices: An observational study based on the global burden of diseases. BMJ Open 9: e028461.
4. Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, et al. (2017) Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: A systematic analysis for the global burden of disease study. JAMA Oncol 3: 524-548.
5. (2020) Breast cancer: prevention and control.
6. Bray F, Ferlay J, Laversanne M, Brewster DH, Gombe Mbalawa C, et al. (2015) Cancer incidence in five continents: Inclusion criteria, highlights from volume X and the global status of cancer registration. Int J Cancer 137: 2060-2071.
7. Nadia Harbeck, Frédérique Penault-Llorca, Javier Cortes, Michael Gnant, Nehmat Houssami, et al. (2019) Breast Cancer. Nature Reviews 5: 66.
8. Iqbal J, Ginsburg O, Rochon PA, Sun P, Narod SA (2015) Differences in breast cancer stage at diagnosis and cancer-specific survival by race and ethnicity in the United States. JAMA 313: 165-173.
9. Fouad TM, Kogawa T, Liu DD, Shen Y, Masuda H, et al. (2015) Overall survival differences between patients with inflammatory and noninflammatory breast cancer presenting with distant metastasis at diagnosis. Breast Cancer Res Treat 152: 407-416.
10. Smith I (2006) Goals of treatment for patients with metastatic breast cancer. Semin Oncol 33: S2-S5.
11. (2020) American Cancer Society.
12. Wang R, Zhu Y, Liu X, Liao X, He J, et al. (2019) The Clinicopathological features and survival outcomes of patients with different metastatic sites in stage IV breast cancer. BMC Cancer 19: 1091.
13. TA King, J Lyman, M Gonen, S Reyes, E-S Hwang, et al. (2016) A prospective analysis of surgery and survival in stage IV breast cancer (TBCRC 013). J Clin Oncol.
14. Petrelli F, Barni S (2012) Surgery of primary tumors in stage IV breast cancer: An updated meta-analysis of published studies with meta-regression. Med Oncol 29: 3282-3290.
15. Harris E, Barry M, Kell MR (2013) Meta-analysis to determine if surgical resection of the primary tumor in the setting of stage IV breast cancer impacts on survival. Ann Surg Oncol 20: 2828.
16. Xie Y, Lv X, Luo C, Hu K, Gou Q, et al. (2017) Surgery of the primary tumor improves survival in women with stage IV breast cancer in southwest China: A retrospective analysis. Medicine 96: e7048.
17. Shien T, Doihara H (2014) Resection of the primary tumor in stage IV breast cancer. World J Clin Oncol 5: 82-85.
18. Rashid OM, Nagahashi M, Ramachandran S, Graham L, Yamada A, et al. (2013) Resection of the primary tumor improves survival in metastatic breast cancer by reducing overall tumor burden. Surgery 153: 771-778.
19. Karnoub AE, Dash AB, Vo AP, Sullivan A, Brooks MW, et

al. (2007) Mesenchymal stem cells within tumor stroma promote breast cancer metastasis. Nature 449: 557-563.

20. Groheux D, Giacchetti S, Delord M, Hindié E, Vercellino L, et al. (2013) 18F-FDG PET/CT in staging patients with locally advanced or inflammatory breast cancer: Comparison to conventional staging. J Nucl Med 54: 5-11.

21. Di Meglio A, Freedman RA, Lin NU, Barry WT, Metzger-Filho O, et al. (2016) Time trends in incidence rates and survival of newly diagnosed stage IV breast cancer by tumor histology: A population-based analysis. Breast Cancer Res Treat 157: 587-596.

22. Ruiterkamp J, Ernst MF (2011) The role of surgery in metastatic breast cancer. Eur J Cancer 3: S6-S22.

23. Lopez-Tarruella S, Escudero MJ, Pollan M, Martín M, Jara C, et al. (2019) Survival impact of primary tumor resection in de novo metastatic breast cancer patients (GeicAM/el Alamo Registry). Nature Res Sci Rep 9: 20081.

24. Tosello G, Torloni MR, Mota BS, Neeman T, Riera R (2018) Breast surgery for metastatic breast cancer. Cochrane Database Syst Rev 3: CD011276.

25. Badwe R, Hawaldar R, Nair N, Kaushik R, Parmar V, et al. (2015) Locoregional treatment versus no treatment of the primary tumor in metastatic breast cancer: An open-label randomised controlled trial. Lancet Oncol 16: 1380-1388.

26. Soran A, Ozmen V, Ozbas S, Karanlik H, Muslumanoglu M, et al. (2018) Randomized trial comparing locoregional resection of primary tumor with no surgery in stage IV breast cancer at the presentation (Protocol MF07-01). Ann Surg Oncol 25: 3141.

27. Fitzal F, Bjelic-Radisic V, Knauer M, Steger G, Hubalek M (2019) Impact of breast surgery in primary metastasized breast cancer: Outcomes of the prospective randomized phase III ABCSG-28 POSYTIVE Trial. Ann Surg 269: 1163-1169.

28. Fisher B, Saffer EA, Deutsch M (1986) Influence of irradiation of a primary tumor on the labeling index and estrogen receptor index in a distant tumor focus. Int J Radiat Oncol Biol Phys 12: 879-885.

29. Fisher B, Gunduz N, Coyle J, Rudock C, Saffer E (1989) Presence of a growth-stimulating factor in serum following primary tumor removal in mice. Cancer Res 49: 1996-2001.

30. Coleman WB, Tsongalis GJ (2002) The molecular basis of human cancer. Spring Sc & Bussis Media Pub. NewYork.

31. Cameron D (2015) Removing the primary tumor in metastatic breast cancer. Lancet Oncol 16: 1284-1285.

32. Cardoso F, Costa A, Senkus E, Aapro M, André F, et al. (2017) 3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). Ann Oncol 28: 16-33.

33. Early Surgery or Standard Palliative Therapy in Treating Patients With Stage IV Breast Cancer.

34. Tadahiko Shien, Tomonori Mizutani, Kiyo Tanaka, Takayuki Kinoshita, Fumikata Hara, et al. (2017) A randomized controlled trial comparing primary tumor resection plus systemic therapy with systemic therapy alone in metastatic breast cancer (JCOG 1017 PRIM-BC). Journal of Clinical Oncology 35.