

Oligometastatic breast cancer: A mini review

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ABSTRACT

With few exceptions such as germ cell tumors, trophoblastic neoplasms and colonic cancers, metastatic solid tumors are considered largely incurable. It is increasingly appreciated that oligometastatic cancer differs from multi-metastatic disease in prognosis and survival. Oligometastatic breast cancer (OMBC) is, therefore, sometimes considered as an intermediate biological state between localized and widely metastatic disease. There is no strict definition of OMBC with studies using different criteria. Treatment of OMBC is still controversial in view of sparse data that is retrospective. However, there is an increasing shift toward individualized, multidisciplinary management of OMBC with the intent to cure some patients. This article will concisely review the subject of OMBC from points of view of biology and practical management recommendations.

Key words: *Oligometastasis, breast cancer, cure*

INTRODUCTION

Metastatic breast cancer (MBC) is generally considered incurable but advances in treatment coupled with stage migration due to improved imaging and diagnostics has resulted in significantly longer survival in the last few years.^[1,2] OMBC is a subset of MBC with limited number and sites of metastasis and constitutes as high as 20% of all MBCs.^[3] There is increasing evidence that prolonged disease control is possible in patients with OMBC when treated with aggressive multidisciplinary management.^[4,5] It is still debatable whether long term survival in this subset is due to selection of patients whose tumors have indolent disease biology or to effects of therapy. The sparse data, heterogeneity of disease biology and absence of randomized trials make treatment recommendations less evidence based.

BIOLOGICAL BASIS OF OLIGOMETASTATIC BREAST CANCER

Metastasis is a series of steps involving complex interactions between the tumor cells, microenvironment and host. Genetic, epigenetic and host immune processes contribute to the balance that is permissive of metastasis. Genes

that are responsible for efficient metastasis have been recently characterized as initiator, progression and virulent genes.^[6] Metastasis “initiation” genes provide selective survival or growth advantage to the primary tumor cells; “progression” genes are those that facilitate rate-limiting functions in colonization; and ‘virulence’ genes are those that provide an advantage in metastatic colonization and growth but not necessarily in the primary tumor. Deficiency in one or more of these pathways could potentially lead to impaired but not completely abrogated metastatic capacity in tumor cells and could constitute the biological substrate of oligometastatic disease. In this model, the rationale for eradication of oligometastatic disease would be premised on preventing further clonal evolution leading to the acquisition of full potential for widespread metastases. Evidence of evolution of oligometastasis phenotype comes from various clinical and preclinical studies. Fidler *et al.* showed differential metastatic ability of different tumor-cell clones derived from B16F1 melanoma lines to colonize the lungs in syngenic mice.^[7] Similarly, differential metastatic activity and clonal heterogeneity have been demonstrated in other cell lines.^[8,9]

Oligometastatic phenotype and behavior are generally consistent with cell lines of low malignant potential and their *in vivo* counterparts could potentially give rise to oligometastatic disease. Genomic instability was initially recognized as a hallmark of cancer development but in last few years it has also been shown to be involved in cancer progression and metastasis. Yachida *et al.* demonstrated the accumulation of sequential hierarchical genetic changes from primary pancreatic tumor formation through its

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DOI:
10.4103/0971-5851.142035

metastatic progression.^[10] This temporal acquisition of genetic changes suggests that some oligometastatic tumors that have less than fully evolved metastatic repertoire could be amenable to potentially curative treatment consistent with their biology. Recent improvements in sensitivity and sophistication of imaging technology have led to increasing detection of oligometastatic disease, some of it in evolution to full metastatic picture and some destined for indolent, non-progressive behavior.^[11] The continuing challenge is to discover biomarkers that will segregate, at diagnosis, the preceding groups of patients with oligometastatic disease, with obvious therapeutic implications.

TREATMENT OF OLIGOMETASTATIC BREAST CANCER

These patients can be clinically divided into those with upfront presentation as OMBC and those with OMBC at relapse. The goals of treatment in MBC are conventionally considered to be increased survival and better quality of life. However, in subsets of patients, such as those with OMBC, the surrogate goals are increasingly changing to complete remission (CR) at clinical or cellular levels. In this context, because of lack of proven progression to clinical disease in all cases, cellular CR cannot be considered to be a clinically relevant end point.^[12]

Chemotherapy as a single modality

There is no study that has systematically evaluated the chemotherapy alone for patients with OMBC. Greenberg *et al.* retrospectively reviewed 1581 MBC patients, mostly chemotherapy naïve, who were treated with anthracycline and alkylating agents based regimens of whom 1293 (82%) had 1-3 metastatic sites.^[13] After completion of treatment, 3.1% of all patients remained in CR for more than 5-year of whom 92% had oligometastatic (1-2 sites) disease at baseline. This suggests a somewhat higher propensity for OMBC to attain long term remissions and functional cures.^[13] This study along with others suggests that patients with low tumor burden metastatic disease are likelier to achieve CR, in turn implying that long term survival was related to low tumor burden/OMBC.^[14] It remains unclear whether long term survival is due to chemotherapy or favorable disease biology or their interaction. A randomized trial addressing this issue will be difficult to implement because of obvious reasons.

High-dose chemotherapy for oligometastatic breast cancer

High-dose chemotherapy (HDCT) followed by autologous peripheral blood progenitor cell rescue has been compared with conventional chemotherapy in patients with MBC in many trials, but the approach remains controversial. The Cochrane review included six randomized controlled trials

(RCTs) demonstrating a significantly improved event-free survival (EFS) at 3, 4, and 5 years after treatment with HDCT, but no overall survival (OS) benefit.^[15] Similarly, a recent meta-analysis of 15 trials that included data on 6210 patients showed significant EFS benefit but none in OS, in favor of HDCT.^[16]

Data for OMBC treated with HDCT is sparse. Nieto *et al.* reported a prospective study of 60 OMBC patients who received induction chemotherapy followed by local treatment followed by hematopoietic stem cell transplantation (HSCT).^[17] The 5-year relapse free survival was 52% in this population. Bojko *et al.*, in a similar small prospective study involving OMBC patients treated with induction chemotherapy followed by local treatment followed by HSCT, reported a 5-year progression free survival (PFS) of 27%.^[18] The difference in outcomes between the two preceding studies could be explained by inclusion of patients with liver metastases (29%) in the second study. Although the results are encouraging, based on these small nonrandomized studies no recommendations can be made regarding the use of HSCT in OMBC patients. Future studies should aim at evaluating the molecular characteristics of patients who may benefit from this treatment.

Surgery of the primary site in oligometastatic breast cancer

The potential advantages of removing the primary tumor in OMBC is elimination of a potential source of further metastatic seeding, restoration of immune competence and reduction in chemoresistance by reducing the number of clones.^[19] Arguments against removal of the primary tumor include Fisher's mouse experimental model which suggested increase in the proliferation of distant tumor foci ("metastasis") associated with the removal of primary tumor masses in different tumor types.^[20]

Until recently there were several retrospective series that showed benefit of local treatment of the primary tumor but these studies included selected patients with better performance status, less advanced primary tumor and lower disease burden. It is difficult to ascribe the outcomes to local treatment versus disease biology in these reports.^[21]

Badwe *et al.* conducted a RCT to address this issue.^[22] In the overall study population ($N = 350$) of patients with MBC who were responding to anthracycline based chemotherapy, they found no benefit of loco-regional therapy (LRT) in terms of OS. In a preplanned subset of patients with oligometastatic (≤ 3) disease there was no difference in OS between the LRT and no LRT arms. Until the presentation of further randomized results, this remains

the best evidence on this question and routine surgery for the primary tumor cannot be recommended in OMBC.

Role of surgery/local therapy of metastatic sites

Again, there is sparse evidence for metastatectomy in patients with OMBC. The largest retrospective data comes from International Registry of Lung Metastasis, which was established in 1991 to collect the experience of curative intent surgery for pulmonary metastases. Among breast cancer patients ($N = 467$) who underwent metastatectomy, the median survival was 35 months with 15-year survival of 18%.^[23] Being retrospective and nonrandomized this data suffers from the same biases that were earlier pointed out for local therapy in such cases.^[19] Although evidence remains inconclusive about its therapeutic value, pulmonary metastatectomy does have a useful role in the confirmation of diagnosis in some patients. Rena *et al.* evaluated a series of 79 consecutive patients who underwent surgery for solitary pulmonary nodule after a curative resection for breast cancer.^[24] Histopathological evaluation of the resected specimen revealed primary lung cancer in 38 patients, pulmonary metastasis from breast cancer in 27 and benign conditions in 14.

Unlike pulmonary resection, liver resection is practiced less often but multiple retrospective analyses in highly selected group of patients show favorable long term survival. Other techniques of local control like stereotactic body radiotherapy and radiofrequency ablation are being increasingly used, but their role is not yet clear.^[11,19]

Thus, metastatectomy in OMBC for therapeutic benefit is not considered standard of care but may be undertaken in individual cases especially to rule out other diagnoses.^[25]

Role of adjuvant or pseudoadjuvant systemic therapy

Borner *et al.* reported the first randomized trial in OMBC wherein patients ($N = 167$) with ‘good-risk’ isolated locoregional recurrence (ILRR) were randomized, after local treatment, to receive tamoxifen or not.^[26] Tamoxifen improved the median disease free survival (DFS) from 26 to 82 months ($P = 0.007$) but OS was not significantly increased, perhaps because of small sample size and short follow-up.

Chemotherapy in the so called “pseudoadjuvant” setting has been supported mainly by phase II trials. The largest data is from M. D. Anderson Cancer Center which published the outcome of patients in four phase II trials utilizing combined modality for the treatment of isolated recurrences.^[4] Patients received local therapy with curative intent and efficacy of “adjuvant” chemotherapy in subjects with clinical CR was evaluated. Three of the 4 studies used doxorubicin based chemotherapy and after a median

follow-up of 121.5 months the estimated 20-year DFS and OS were both 26% in these studies. With a shorter median followup in the docetaxel based trial, the DFS was 58%. However, potential selection bias and inclusion of anthracycline and taxane naïve patients in these studies makes their results less generalizable.

The recently published CALOR trial also sheds light on the benefit of chemotherapy in completely resected ILRR of breast cancer.^[27] Patients ($N = 162$) were randomized to chemotherapy ($N = 85$) versus no chemotherapy arm ($N = 77$) and a choice of chemotherapy was left to investigator discretion. Chemotherapy reduced both distant and second local failures, and 5-year DFS was 69% in the chemotherapy group when compared to 57% in no chemotherapy group ($P = 0.046$). In a prespecified subgroup analysis, adjuvant chemotherapy seemed to be significantly more effective in women with estrogen-receptor-negative ILRR patients assigned to chemotherapy for estrogen-receptor-negative ILRR, but the interaction test was not significant. The authors concluded that ‘adjuvant’ chemotherapy could be recommended in completely resected ILRR, especially if the tumor was ER negative.

Role of neoadjuvant like chemotherapy

Extrapolating from non-MBC the option of upfront chemotherapy followed by local therapy in responding OMBC patients could be explored. The potential advantage of this strategy could be exclusion of patients with chemoresistant disease (and potentially poor outcomes) from local therapy. Kobayashi *et al.* have recently published a retrospective analysis of patients ($N = 75$) treated with this strategy and the experimental arm of Badwe *et al.* also utilized the same treatment plan.^[5,22] In the former study, at a median follow-up of 103 months, the estimated 10- and 20-year OS rates were 59.2% and 34.1% respectively. These results can, at least partly, be explained by selection of good prognostic patients (60% with metastasis in one organ and 40% chemotherapy naïve).

CONCLUSION

Oligometastatic breast cancer is a subgroup of patients with MBC who have good long term survival raising the tantalizing possibility of “functional cure.” However, it is still uncertain whether these ‘cures’ are due to selection of patients with favorable disease biology versus ‘aggressive’ local or systemic therapeutic interventions. The increasing sensitivity and sophistication in detection of metastatic disease is likely to increase the number of OMBC patients. Depending on a number of host and tumor characteristics, at least some of these patients are candidates for

multi-modality therapy. Archived tumor tissue from long term OMBC survivors is likely to be a valuable resource in dissecting the biology of these tumors compared to patients with multi-metastatic disease. Collaborative efforts at clinical, pathological and molecular data collection are therefore very much in order.

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How to cite this article: Rastogi S, Gulia S, Bajpai J, Ghosh J, Gupta S. Oligometastatic breast cancer: A mini review. *Indian J Med Paediatr Oncol* 2014;35:203-6.
Source of Support: Nil. **Conflict of Interest:** None declared.