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Surgical Management of de novo Stage IV Breast Cancer

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The natural history of stage IV breast cancer is changing, with diagnosis when the disease burden is lower and better drugs translating into longer survival. Nevertheless, a small but constant fraction of women present with de novo stage IV disease and an intact primary tumor. The management of the primary site in this setting has classically been determined by the presence of symptoms, but this approach has been questioned based on multiple retrospective reviews reported over the past decade that suggested a survival advantage for women whose intact primary tumor is resected. These reviews are necessarily biased, as younger women with lower disease burden and more favorable biological features were offered surgery, but they led to several randomized trials to test the value of local therapy for the primary tumor in the face of distant disease. Preliminary results from 2 of these do not support a significant survival benefit, although local control benefits may exist. Completion of ongoing trials is needed to reach a definitive conclusion regarding the merit of primary tumor resection for local control and survival. Until unbiased data are available, local therapy for asymptomatic primary tumors cannot be recommended in the expectation of a survival benefit.
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Introduction

Metastatic breast cancer is considered to be a fatal disease, regardless of whether distant metastases are discovered at initial presentation (de novo stage IV) or following apparently successful therapy of localized disease and an intervening disease-free interval (DFI) (metachronous stage IV). In both the situations, the primary and most important treatment modality is systemic therapy, initiated as either endocrine or cytotoxic agents, with or without human epidermal growth factor receptor (HER)-2–directed or other targeted therapies.[1] Recent rapid advances in medical therapy, with the discovery of new therapeutic targets, and drugs directed at these targets, has led to the concept of stage IV breast cancer as a chronic disease. With this ever-increasing medical therapy armamentarium, and perhaps with better palliative care, survival of patients with stage IV breast cancer has improved steadily over the past 2 decades.[2] Consequently, the question of management of the primary tumor in women with de novo stage IV breast cancer has attracted significant interest, particularly as loss of control at the primary site can have a profound effect on the quality of life. Similar questions apply to patients with metachronous stage IV disease that is accompanied by recurrence in the conserved breast.

Approximately 5% of women with primary breast cancer in the United States and Western Europe present with de novo stage IV breast cancer,[3] with larger fractions in other parts of the world. Retrospective data published over the past decade suggest that primary tumor resection (and possibly radiotherapy [RT]) may improve survival when used in conjunction with effective systemic therapy. These data, along with the relative lack of morbidity of breast surgical procedures, have led to some enthusiasm for the resection of asymptomatic primary tumors, in contrast to the classical approach of reserving resection for palliation of symptomatic primary tumors. The evidence for resection of the intact primary tumor in women with metastases is discussed later, with emphasis on the emergence of new prospective data that would likely drive reevaluation of this question.

Trends in Survival of Patients With Stage IV Breast Cancer

There have been several studies indicating improvement in survival of women with metastatic breast cancer over the past 3

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decades.[2,4,5] A single-institution review of women diagnosed with metastatic disease treated from 1974-1979 showed a median survival of 15 months compared with those treated from 1995-2000 who had a median survival of 58 months (ref). Similarly, Andre et al[2] reported temporal trends in improvement of survival for patients with metastatic disease based on treatment period, comparing the intervals 1994-2000 and 1987-1993. Although some of these improvements are undoubtedly because of better systemic therapy, lead time bias related to more sensitive imaging and therefore earlier diagnosis of metastatic disease in later periods are also likely contributing factors, given the retrospective nature of these studies. More recently, Dawood et al[5] examined the outcomes between patients with de novo stage IV breast cancer and those who experienced metachronous distant relapse. From a large cohort of patients examined from a single institution, they found the median survival for patients who presented with de novo stage IV breast cancer was 12 months longer than in women with relapsed breast cancer. This difference was statistically significant in both univariate and multivariate analyses. The authors also noted that DFI was also associated with outcomes. Specifically those patients whose disease relapsed with shorter DFI had worse outcomes when compared with those patients who presented with de novo stage IV disease. The reasons for this difference in outcomes may be partially related to the fact that women with de novo stage IV disease are treatment naïve and therefore may respond better to systemic therapy, whereas those with metastatic relapse have demonstrated therapeutic resistance of their tumors. There may also be biological differences dictated by the presence of the primary tumor in de novo stage IV disease, as suggested by Folkman et al,[6] vs reactivation of dormant, resistant clones in metachronous metastases; however, present knowledge regarding interactions between the primary tumor and metastatic sites in humans, and any influence these may have on the course of disease, is limited.

Reasons to Question the Classical Paradigm

Evidence has accumulated over the past 15 years, to suggest that a reduction in tumor burden at the primary site may add to the efficacy of systemic therapy and aid survival. These include a randomized trial of patients with de novo stage IV renal cell carcinoma, which demonstrated a modest but significant survival advantage for the nephrectomy group.[7] An improved survival with resection of primary disease with or without resection of distant disease has also been observed in metastatic ovarian, colorectal, and gastric cancers. Particularly in ovarian cancer, tumor debulking in the abdominal cavity has become a standard component of overall treatment strategy, despite the lack of a randomized trial testing this approach. Thus, based on retrospective data, these cancers are frequently managed with tumor debulking before chemotherapy,[8-13] drawing on the theory that a smaller tumor burden increases the efficacy of chemotherapy.[14]

Theoretically, a benefit from resection of the primary tumor in patients with overt metastases can be supported along several lines, ranging from its potential role as a source of tumor stem cells with enhanced metastatic potential[15,16] to the possibility that tumor-induced immunosuppression is facilitated by the intact primary tumor.[17,18] Conversely, there has been a concern, based on laboratory data, that primary tumor resection may accelerate the growth of metastatic lesions, but this has not been demonstrated in humans. Although these laboratory data suggest a biological basis for improved survival with resection of the primary tumor in the setting of metastatic disease, these specific models have not been validated in humans.

The Retrospective Data on Primary Tumor Resection or RT

Potential for Benefit

Following the publication of a randomized trial demonstrating the value of primary tumor resection in stage IV renal cell carcinoma, a number of retrospective studies were performed to examine the effect of surgical resection of the primary tumor on survival in the setting of metastatic breast cancer.[19-33] These studies have come from single institutions and large databases from the United States, Europe, and Asia. The type of local therapy has largely been surgery alone (evaluated in more than 18 studies), although a few authors have been able to evaluate surgery plus RT.[34-36] The survival outcomes in these retrospective analyses have been the subject of several reviews and meta-analyses.[37-40] A recent meta-analysis by Petrelli and Barni[38] included 15 retrospective case series and found that surgery of the primary tumor was independently associated with longer survival, with a hazard ratio (HR) of 0.69 ($P < 0.00001$). The survival benefit was independent of age, tumor burden, type of surgery, margin status, site of metastases, hormone receptor status, and HER2 status; the use of systemic therapy and RT was significantly associated with survival. Owing to a variety of reasons, 9 studies were excluded.

A similar literature has developed on the use of primary RT for the primary site, showing a similar magnitude of survival benefit. The RT studies have come mainly from single institutions in France and Canada. The first and largest was reported by Le Scodan et al.[34] These investigators identified 581 patients with de novo stage IV breast cancer treated between 1984 and 2004, 320 of whom received locoregional RT, with 41 women receiving both surgery and RT and 30 receiving only surgery. Nodal fields were included for most patients, and most of those receiving RT were given a boost dose to the tumor site. The overall survival rate was 43% in the group receiving locoregional therapy vs 27% in those who did not, for an adjusted HR = 0.7 (95% CI: 0.58-0.85). A second French study of 236 patients described similar differences in outcomes with the use of primary RT to the primary site, but adjusted estimates of overall survival showed no significant advantage for the primary site local therapy (PSLT) group.[35]

The value of postoperative (as opposed to primary) RT has been difficult to assess in these retrospective studies, as large databases such as the National Cancer Data Base (NCDB) and the Surveillance, Epidemiology, and End Results (SEER) did not distinguish between RT to the primary and metastatic sites. The data that are available do not allow clear conclusions and