Is Removal of the Primary Tumor Beneficial in Breast Cancer with Synchronous Metastases? – There May Be More than One Answer

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Six percent of women newly diagnosed with breast cancer have stage IV disease, representing 3,000 new cases per year in Germany and 19,000 in the EU [1]. Currently, metastatic breast cancer (MBC) is considered an incurable disease. Since efforts to achieve an improvement in survival by systemic therapy have been extensive but mostly frustrating, maintaining a high quality of life for a long time is currently the primary focus. As a consequence, treatment of MBC including local therapy of the primary tumor is aimed at symptom control. However, recent retrospective studies from single institutions and from large centralized, population-based databases have challenged this approach and suggest that local control of the primary tumor either by surgical excision or irradiation is associated with better survival in breast cancer patients with synchronous metastases [2, 3]. In a Dutch systematic review of the literature the pooled overall mortality benefit was 35% in favor of the patients undergoing surgery (hazard ratio 0.65; 95% CI 0.59–0.72) [2]. However, currently data suffer from the fact that there are only retrospective analyses available and, on the other hand, not all studies addressing this subject have reported a favorable prognosis for the patients undergoing local treatment. The article by Rosche et al. in this issue of ONKOLOGIE [4] casts more doubt on the benefit of locoregional therapy. These investigators suggest that the advantageous effect seen in other studies may be the result of selection bias.

Understanding of the molecular mechanisms of metastasis is very limited. According to the common model of metastasis the primary tumor is biologically heterogeneous and its metastatic potential is determined by subpopulations of cells that acquire genetic alterations and thereby facilitate metastatic spread [5]. An indispensable part of this model are circulating tumor cells (CTCs) that may settle on the right soil and become dormant. Dormant cells show no evidence of multiplication for long time, yet retain their capacity for vigorous reproduction and, in the presence of a favorable microenvironment, develop into metastases.

The research of a century has produced abundant evidence for a very complex interaction between primary tumor, dormant tumor cells, and metastases [3, 5]. It has been demonstrated that the primary tumor maintains tumor homeostasis. It influences tumor growth by shedding enhancers and inhibitors of angiogenesis and their balance is crucial for neovascularization. In experimental models the primary tumor controls metastatic growth by suppression of new blood vessel formation and its removal leads to an increase in number and size of metastases. The primary tumor also affects the equilibrium between tumor replication and cell death, a mechanism underlying tumor dormancy. Furthermore, it can induce an immunosuppressive state and influence metastatic disease progression possibly owing to cytokine secretion.

In this context an advantageous effect of loco-regional treatment might be triggered by several mechanisms [3, 5]: i) reduction of the total tumor burden may increase the effectiveness of chemotherapy by removing necrotic tissue and nonvascularized tumor cells; ii) removal of the primary tumor may limit an additional reseeding of tumor cells; iii) the surge of angiogenesis at distant metastatic sites after excision of the primary tumor may enhance chemosensitivity; iv) eliminating breast cancer stem cells from the primary tumor may limit the emergence of chemoresistant cell lines; v) removal of the primary tumor helps to restore immunity and to improve nutritional status; vi) local control prevents chest wall and in-breast disease, which are known to detrimentally influence survival. Resection of the primary tumor has been linked to better survival in other metastatic malignancies including renal carcinoma, stomach, colon, and ovarian cancer, and melanoma [3].

Adversely, removal of the primary tumor may initiate a burst of tumor growth by interruption of metastatic breast cancer dormancy in particular through angiogenic switch. In addition surgical wounding is known to release growth and immunosuppressive factors which may stimulate tumor growth [5].

Thus by modulating tumor dormancy removal of the primary breast cancer might have both beneficial and adverse effects upon cancer spread and growth. Therefore, future research may not provide a simple answer to the question whether removing the primary tumor benefits patients with metastatic breast cancer at first presentation. The following are only some of the unresolved issues: i) optimal timing of surgery; ii) relevance of clear margins; iii) impact of axillary clearing; iv) role of radiation therapy; v) identification of patient subgroups most likely to profit, e.g. by metastatic pattern, endocrine situation, tumor properties, or response to systemic therapy.

Regardless of the findings, all of the scientific papers dealing with this subject have one statement in common: 'prospective trials which are less prone to data bias are urgently needed'. Such a study is under discussion among USA and European cooperative groups and 2 randomized trials, one sponsored by the Turkish Federation of the National Societies for Breast Diseases and the other by Tata Memorial Hospital, India, are ongoing [3]. Hopefully their results will bring some answers to the pending questions.

The Turkish trial (NCT00557986) is intended to enroll 271 patients in a comparison of upfront surgery including axillary

staging with systemic therapies (study group) and systemic therapy only (control group). Controls will only receive surgery to cope with local complications. The primary endpoint is mortality and the secondary endpoint is the assessment of quality of life. The estimated completion is October 2012. The Indian trial (NCT00193778) should enroll 350 patients in a comparison of locoregional therapy (i.e. surgery and adjuvant radiotherapy if indicated) and no locoregional therapy, given after 6 cycles of anthracycline based chemotherapy. Primary endpoints are time to progression and overall survival and secondary endpoints are correlative findings, such as change in angiogenic factors. The estimated study completion date is June 2012. In a preliminary report of this trial (125 patients: 53 patients randomized to surgery and 72 patients randomized to observation; median follow-up 18 months), surgery of the primary tumor was not associated with better progression-free or overall survival [3].

Disclosure Statement

The author declares that there are no conflicts of interest.

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