

Primary Tumor Surgery in De Novo Metastatic Breast Cancer: An Unresolved Controversy

Opinion

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Ximena Briceño-Morales^{1*}, Clara Briceño-Morales^{1,2}

¹Instituto Nacional de Cancerología, Bogotá, Colombia

²Universidad Militar Nueva Granada, Bogotá, Colombia

*Corresponding author

Ximena Briceño-Morales, Instituto Nacional de Cancerología, Bogotá, Colombia

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Opinion

Breast cancer represents the leading cause of cancer incidence and mortality in women worldwide [1]. By 2020, about 2.3 million new cases were diagnosed, which constitutes 24.5% of all cancers. It is shocking to recognize that, in women, one in four cancers corresponds to breast cancer [2].

Despite advances in the early diagnosis of breast cancer, thanks to mammography screening and new techniques to perform this test [3–6], a not inconsiderable percentage of women are still diagnosed in advanced stages. In high-income countries like the United States, about 6% of patients are diagnosed in stage IV, in contrast to 25% of patients diagnosed in some low- and middle-income countries [7,8]. Even so, the prognosis of metastatic breast cancer has improved in recent decades, in 1985 the 3-year overall survival was 27%, while by 2000 it had increased to 44% [9]. There are even authors who affirm that women with de novo metastatic breast cancer have better outcomes than those with recurrent disease [10,11], in whom median overall survival can be found between 39 and 48 months [12,13]. This dramatic improvement in survival is fundamentally attributed to advances in systemic therapy, leaving little or no space to locoregional treatments, which have been relegated to the symptomatic control of the disease [7,14].

Despite the above, the controversy that exists about the role of primary tumor surgery in patients with de novo metastatic breast cancer remains current. The results of the studies are contradictory. On the one hand, the lower-quality evidence, mostly from retrospective observations, shows that resecting the primary tumor may offer a relative survival advantage [14]. Classic studies such as those by Khan [15], Fields [16], Gnerlich [17] and Blanchard [18], among others, noted that patients with de novo metastatic disease who underwent primary tumor surgery had lower mortality than those

who did not. However, strong criticisms have arisen regarding the validity of this information, since the methodological design of these studies is deficient, as they present multiple confounding factors and selection biases, among those that stand out, choosing for surgery only those women with good prognostic factors (young, with fewer comorbidities, with non-visceral disease, smaller tumors, more favorable tumor biology and histology, and with adequate response to previous systemic treatment) [7,14,19]. Furthermore, it is difficult to group these studies because they are heterogeneous, and differ in the number of patients, the indication and the time of surgery, as well as the type of surgical intervention [19,20]. Then, it is questioned whether it is pertinent to modify such a radical therapeutic approach based on said information.

On the other hand, the results of randomized clinical trials (RCTs) have not been able to confirm the presumed benefit of primary tumor surgery. In fact, Badwe [19] and Fitzal [21] found that this intervention was associated with an increased risk of distant progression, and Khan [22] that it could contribute to the detriment in the health-related quality of life of patients. The latter was paradoxical since it has always been considered that with resection of the primary tumor symptoms such as pain, ulceration, bleeding and tumor necrosis are alleviated [23]. The study by Soran [24] is the only RCT that has shown that primary tumor surgery prolongs survival in women with de novo metastatic disease. In this study, there was a 34% decrease in the risk of dying in patients undergoing surgery (HR 0,66; 95% CI: 0,49-0,88). But, again, criticism of this study is multiple due to the deficient stratification by prognostic factors between the comparison groups, and the lack of histopathological confirmation of metastatic disease [7].

At this point, it would be easy to simplistically conclude that primary tumor surgery has no role in the management of de novo metastatic breast cancer. However, in defense of those who continue to advocate

this surgical procedure, it should be mentioned that RCTs that are negative also have methodological problems that are not negligible. In the study by Badwe, patients with a high burden of distant disease were included (85% with more than 3 metastatic lesions), and only about 30% had exclusive bone disease. Additionally, the chemotherapy regimen administered was outside current standards and only 8% of patients with HER2-positive tumors received trastuzumab, suggesting that the poor outcomes in both groups (surgery and not surgery of the primary tumor) were a consequence of suboptimal cancer treatment [7,14] and therefore the contribution of surgery in this setting cannot be objectively evaluated. In the studies by Fitzal [21] and Khan [22], of which only preliminary versions are available, the expected number of patients was not recruited and they were prematurely closed, without clarity about a possible adjustment to the statistical analyzes of the evaluated results. It is not easy to design a RCT capable of including all the variables to consider in this disease, and with a sufficient number of participants to perform subgroup analysis for all important outcomes. New prospective studies are unlikely to clear up any doubts on this issue.

It is necessary to mention at this point that neither retrospective studies nor RCTs have had sufficient statistical power to analyze certain subgroups of women who may eventually benefit from primary tumor surgery. This is the case of patients with hormone receptor-positive or HER2-positive tumors, for whom there is highly effective systemic therapy, which allows achieving median global survival of between 4 and 5 years [25]. Although there is retrospective information that shows that among patients with an adequate response to systemic therapy, surgery of the primary tumor does not offer any survival advantage [26], since the benefit is obtained from systemic treatment and not from surgery. There is also retrospective information that affirms that, even in the presence of hormonal or antiHER2 therapy, women with de novo metastatic breast cancer could have better outcomes when the primary tumor is resected [27]. With this evidence, it remains uncertain which biological subtypes benefit from surgery.

Another element of debate is the fact that there is growing literature that indicates that certain locations of metastatic disease may have a less aggressive behavior, such as when there is exclusive involvement in bone, contralateral axilla, skin or soft tissues. Patients with metastases in these sites show better breast cancer-specific survival rates and overall survival [28-30]. Some authors question whether the exclusive involvement of the contralateral axilla should be considered stage IV, since in these cases breast cancer behaves more like a locally advanced disease than a metastatic disease [31]. It is not unreasonable to think that in this context, surgery of the primary tumor can contribute to improving the survival of the patients.

To conclude, de novo metastatic breast cancer differs from recurrent disease [32]. It is a clinical entity whose heterogeneity is demarcated by tumor biology, which offers a differentiated prognosis for each patient [33]. Today the mainstay of treatment continues to be systemic therapy. Regarding surgery of the primary tumor, its role is clearly established for the palliation of local symptoms [7], and, although with the evidence currently available the survival benefit seems to be none, it cannot be completely ruled out that some patients with tumors with a good prognosis, with an adequate response to initial systemic treatment, with mono or oligometastatic disease (mainly in bone) or in unconventional locations (only contralateral axilla, skin or soft tissues), may benefit from surgery. The RCTs were not designed to calculate these differences by subgroups, making it impossible to quantify the point contribution, in terms of survival, of primary tumor surgery in patients who have otherwise responded satisfactorily to initial systemic therapy. The management of this disease should be individualized and ideally carried out by an expert team in breast cancer. The decision to perform surgery on the primary tumor should

always be considered by a Multidisciplinary Board, which should take into account not only traditional cancer outcomes such as progression-free survival and overall survival, but also others such as quality of life and costs related to disease care, outcomes that are increasingly relevant in the oncology field.

Conflict of interest

The authors declare that they have no conflicts of interest.

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