



To resect or not to resect? – the dilemma in oligometastatic breast cancer

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Despite the good prognosis of the vast majority of breast cancer cases, about 10% is firstly diagnosed with stage IV, while 20–30% of localized disease treated with curative intent will eventually relapse (1). Hepatic metastases are the third site of relapse, after lymph-nodes and bone, but, due to the early systemic nature of breast cancer, rarely the recurrence is liver-limited.

In this issue of *HepatoBiliary Surg Nutr*, Grazi reports a systematic review in the attempt to clarify indications, prognostic factors and outcome of liver surgery for breast cancer hepatic metastases (2).

From a theoretical point of view, improvement in imaging techniques, with better patients' selection, and in surgical/ablative procedures, with lower morbidity and higher parenchymal spare, should increase the benefit/risk ratio. This hypothesis is however difficult to be tested in the clinical reality, as randomized trials in this setting are difficult to run.

While in colorectal cancer the role of metastases resection, and of liver resection in particular, is well established, this is not the case in breast cancer. As clearly reviewed by the Author, studies are heterogeneous and inconclusive, and therefore it is not possible to draw a clear, evidence-based indication on the role of liver surgery in this disease. But why all the attempts of researchers to chase down this conundrum seem to remain ineffective?

First of all, the definition of oligometastatic disease is somewhat empirical, generally referring to metastatic breast

cancer presenting or recurring with limited metastatic disease. In the attempt to have a more precise definition, recent guidelines refer to metastatic disease with up to five lesions in total, not necessarily in the same site/organ (3,4). Notably, to be defined as oligometastatic diseases, all lesions should be potentially amenable to local treatment. The situation is even more complicated considering that we have at least 3 different clinical scenarios: (I) synchronous oligometastatic disease, where patients present with stage IV *de novo* disease and oligometastatic spread at initial presentation; (II) metachronous oligometastatic disease, where patients present oligometastatic recurrence after definitive treatment of the primary tumor; (III) induced oligometastatic diseases, where patients with widespread metastatic disease is converted by systemic treatment to a condition of oligometastatic disease (5). Moreover, the scenario of systemic treatment for advanced breast cancer profoundly changed over the last 20 years, further limiting the clinical value of the already scanty literature data, mainly consisting of retrospective series, including heterogeneous patient's populations enrolled over a wide time span, with only a few reporting on systemic treatments.

Indeed, breast cancer is no longer a unique disease, and actual survival scenario is widely different according to molecular subgroups. The availability of new therapeutic options including targeted agents and immunotherapy has dramatically increased the survival of metastatic breast cancer over time (6). In HER2+ disease, the combination

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of pertuzumab-trastuzumab and docetaxel as first line therapy was associated with a median overall survival (OS) of 57 months (7). In HR+ disease, the median OS with the combination of letrozole plus the CDK4/6 inhibitor ribociclib was 64 months (8). Even the more aggressive subtype of breast cancer, the triple negative disease, recently faced an overall survival improvement in the PD-L1 positive subset with the combination of chemotherapy and immunotherapy (median OS for nab-paclitaxel combined with atezolizumab exceeding 25 months) (9). The therapeutic armamentarium is further increase by the availability of PARP inhibitors in case of gBRCA mutations and PI3k inhibitors for patients whose tumors harbor PIK3CA mutations (10-12). Therefore, each molecular subtype has now distinct treatment algorithms, which are regularly updated as soon as new options became available (2). In this rapidly evolving scenario, addressing the clinical utility of metastases resection is particularly challenging. Indeed, few studies on liver resection report survival of resected patients according to the well-known prognostic factors, and systemic treatment administered in these studies are no longer actual. A recently published meta-analysis (13) confirms that positive axillary nodal metastases of breast cancer at resection of the primary tumor, negative estrogen receptors (ER), along with multiple lesions and extra-hepatic disease, are negative prognostic factors also for resection, as for systemic therapies.

In the absence of an ultimate answer to the Shakespearean question “to resect, or not to resect”, have we to completely disregard this option for our patients? We believe this is not the case. First of all, despite not formally recommended by guidelines, many patients undergo spontaneous intensive follow-up, increasing the prevalence of patients diagnosed with limited disease burden, possibly amenable of surgical treatment with curative intent. In addition, more active therapies will favorably impact on disease management over time, selecting patients where a multimodal approach can increase the chance for long-term disease control. In this subset of patients, even if the concept of “drug holidays” is becoming less relevant in view of the generally good safety profile of new therapies, a radical resection, especially if with low invasiveness, might offer the possibility to stay “treatment-free” for a certain period, with positive impact on quality of life.

However, the way to optimize the resective approach requires a fine tuning of patients’ selection, considering not only traditional clinical prognostic factors, but also a better molecular stratification including longitudinal characterization of relapsed disease. A great opportunity

in this perspective is offered by the detection and analysis of tumor circulating free DNA (“liquid biopsy”), already known as important prognostic element in oligometastatic colorectal cancer eligible to metastases resection (14).

An ambitious randomized trial is underway to evaluate the role of standard of care therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical ablation for newly oligometastatic breast cancer (15). The more complex become the disease management, the higher is the importance of the Multidisciplinary Team involvement. Traditionally, its role was well established in discussing and guiding choices in early breast cancer, but the more are options we face also in advanced disease, the more is the need for a shared clinical decision. In the absence of a clear-cut reference literature, only a group of well-prepared specialists on breast cancer can offer the expertise to evaluate case by case the answer to the question: to resect, or not to resect?

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