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Is there a role for locoregional treatment of the primary tumor in de novo metastatic breast cancer in the era of tailored therapies?

Evidences, unresolved questions and a practical algorithm

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Abstract:

Improvements in systemic therapies have changed the face of *de novo* metastatic breast cancer (dnMBC), with a 5-year survival rate exceeding 25%. Increasing evidence suggests that a subset of patients could benefit from a locoregional treatment (LRT) with prolonged survival, although the diversity of publications on the subject make it difficult to draw any conclusions. In this review, we summarize the available data on retrospective, prospective and current ongoing clinical trials. Since factors such as tumor biology, pattern of metastatic dissemination and the timing of the treatment are closely linked to the therapeutic strategy, we focus on papers which include these aspects. We discuss recent studies indicating that exclusive radiotherapy provides results comparable with those obtained by surgery. We will then discuss the biological rationale for LRT. Finally, we propose a decision-tree to select the optimal candidates for LRT in dnMBC patients.

Keywords: *de novo* metastatic breast cancer, surgery, exclusive radiotherapy, locoregional treatment, primary tumor, tumor biology

1. Introduction

Breast cancer (BC) is the most frequent cancer among women worldwide. Five to eight percent of patients present with metastasis at initial diagnosis (stage IV) which is known as *de novo* metastatic breast cancer (dnMBC) (1–3). These patients represent up to 25% of all metastatic breast cancers and have a better prognosis than metastatic relapse (3–5). In addition, new types of management have led to increased overall survival (OS) with 20 to 40% exceeding 5 years (3,6,7). Therefore, the question of locoregional treatment (LRT) for these patients with an intact primary tumor (PT) has arisen as a means not only to control locoregional evolution but also to increase OS. Although no recommendations exist on this topic except to control palliative symptoms, recent large real-world databases from Europe and USA showed that approximately 40% of women undergo LRT in the context of dnMBC (5,7,8). However, this question has been controversial for decades, with many meta-analyses trying to synthesize highly heterogeneous data (9–13).

The question was first addressed from a surgical point of view, leading to the publication of about 10 retrospective studies. The primary aim was to ensure locoregional control, since local evolution of a breast tumor may result in a profound alteration of the quality of life (QoL) (14). Before the 2000s, MBC were not separated into different immunohistochemical (IHC) subtypes (based on Human Epidermal Growth Factor Receptor-2 (HER2) and hormonal receptor (HR) status), and no systemic tailored therapeutic options were available, except endocrine therapy. Nowadays, all therapeutic decisions are based on patient-related factors (age, comorbidities), metastatic dissemination (site and number of metastases) and most importantly tumor biology. Tailored systemic therapies, including targeted therapies and immunotherapy, have led to increased OS in subgroups of patients (15–18). In parallel, radiotherapy (RT) techniques have considerably improved, allowing for the radiation dose to conform more precisely to the three-dimensional shape of the tumor, thus enabling much higher radiation doses and better tumor control with less toxicity (19,20).

Consequently, the LRT of the PT in dnMBC is no longer only a surgical challenge, but more the result of a shared medical decision between medical, radiation and surgical oncologists. It is no longer only a question of locoregional control but rather a wider issue of improving OS, due to the possible biological link between PT and metastases. We discuss herein the question of LRT in dnMBC in the current era of BC IHC subtypes and focus on retrospective studies including enough biological and clinical parameters to be transposed to current practice and issues. We then discuss recent results from prospective studies (published and ongoing) and focus on clinical data involving exclusive RT (ERT) as a therapeutic

modality, as more data are currently available. We next discuss the biological rationale for LRT in metastatic disease including new pre-clinical data available on the immune system and its interaction with tumor cells. We conclude with a proposed algorithm to select the optimal candidates for LRT.

2. LRT or no LRT: evidence and unresolved questions

2.1 Who are de novo metastatic breast cancer patients in 2020?

Although BC screening largely increased the proportion of small localized tumors at diagnosis, the use of more sensitive diagnostic imagery (**computed tomography (CT)-scan or positron emission tomography-CT**) allows for better detection of metastatic lesions. Interestingly, the proportion of dnMBC has remained globally stable over the last decades at around 3 to 8% (2–4), but there are several patterns of dnMBC at diagnosis:

- It could be the early dissemination from the PT, which is sometimes even unknown. Indeed, among dnMBC at diagnosis, 30 to 40% present with a tumor smaller than 5 cm without clinical node involvement in 15-25% (5,7,21). This suggests dissemination from early transformed lesions and acquisition of important genetic changes at the metastatic site, a phenomenon known as parallel progression (22).
- It could be slow growth from a neglected PT, which finally lead to metastatic sites that grow at equal rates (defined as linear progression, since genetic alterations originate mainly from the PT (23)).
- Finally, it could be a quick and aggressive disease phenotype, with an aggressive loco-regional disease with skin nodules on the chest wall that concomitantly develop secondary lesions. Up to 30% of patients with inflammatory BC have metastases at diagnosis (24).

Also, the metastatic burden at diagnosis of dnMBC is heterogeneous and can vary from a mono-metastatic disease to a diffuse multi-metastatic state. A subset of patients are therefore diagnosed with an oligometastatic disease, defined by a limited number and size of metastatic lesions ranging from 1 to 5, not necessarily in the same organ (25). Several large studies in a variety of primary tumor types with oligometastatic dissemination have demonstrated prolonged survival associated with local primary (in the de novo metastatic disease) plus metastases loco-regional treatment (26). As discussed below, these highly heterogeneous patients indistinctly included in retrospective studies will certainly affect the indication, the type and the impact of LRT.

2.2 Heterogeneous retrospective studies prevent homogeneous recommendations

Most clinical data available come from retrospective studies, including large population-based studies involving thousands of patients and smaller mono/multicenter institutional studies (14,27–32) (main studies are listed in Table 1) (5,7,8,14,21,27,29–31,33–58). Five meta-analyses published over the past two decades suggested that PT surgical resection may improve survival with a hazard ratio (HR) around 0.60 (9–13). The most recent one published by Gera *et al.* in 2020 included 42 studies and concluded that surgery would specifically reduce mortality by 36.2% (13). However, several dozens of studies were performed before the era of high-quality imaging to assess metastatic extension, but also before the current IHC classification and systemic tailored therapies, thus limiting their relevancy in the current thinking. Consequently, differences observed in terms of OS between LRT and no-LRT could result from several biases (30,33,49), and from heterogeneity between studies including:

- A very long period of recruitment sometimes spanning more than 40 years and consequently different systemic therapy modalities (before and/or after LRT) (32).
- Indisputable selection bias: women who received surgery tended to be younger and healthier, to have smaller PT, a lower burden of metastatic disease, and were less likely to have visceral metastases (review in (59)).
- Sensitivity to systemic therapy (ST), which could influence the decision to propose LRT and thus local therapy, may serve as a surrogate of systemic response. Clearance of metastases after ST was unknown in retrospective studies, and it is impossible to determine why women went to surgery. Some studies only included patients with a systemic response, while others included all patients at diagnosis. Patients who did not respond to first-line ST would be more likely included in the no-LRT group, thereby biasing this subgroup with a poor prognosis.
- Different treatment modalities between patients within the same study or between studies regarding surgical timing, resection margins, axillary dissection, radiation therapy, primary induction ST and the type of induction therapy.

Identifying the clinical pattern involved in retrospective studies is very challenging, even with robust statistic methods including multivariate regression analysis and/or, in recent years, the addition of propensity analysis (7,21,36,37,60). To limit this bias, it is necessary to select only the patients who had an objective response or a stable disease to the first line of ST and to exclude those who died or progressed quickly after diagnosis (7,8,58). The largest study that specifically tried to control this bias by selecting patients who survived at least 1 year was

published in 2019 (8). Nearly 25000 patients were included: 56% received ST alone, 19% underwent PT surgery before ST and 25% underwent PT surgery after ST. The authors concluded that surgical resection of the PT was associated with improved survival, regardless of the treatment sequence (HR=0.72 and HR=0.58 before and after ST, respectively). Unfortunately, HER2 status was not available in this database.

However, since the prognosis of dnMBC is first linked to metastases, clinical oncologists now widely agree that it is better to initiate a ST, which also has the advantage of testing for sensitivity of the tumor and therefore selecting the optimal patients. Moreover, most of the retrospective studies did not include information about two major indispensable criteria for therapeutic decision-making today: pattern of metastatic disease and IHC profile, both of which have been largely reported as prognostic factors in dnMBC (1,61,62). **Patients diagnosed with oligometastatic disease were mostly not identified, and potential local ablative treatments on metastatic lesions were not reported.**

2.3 Superiority of tumor biology over anatomic dissemination for decision-making: an evolving paradigm

The 5th ESO (European School of Oncology)-ESMO (European Society of Medical Oncology) international consensus guidelines for advanced breast cancer (ABC5) suggested that a multimodal approach, including LRT with curative intent, should be considered for selected metastatic BC patients, especially for the subset of patients with bone-only disease (25). Recent real-world observational studies showed that bone was the most common site of metastasis (around 45% of patients) and up to 30% of patients were diagnosed with bone-only metastases (7,58). A recent, large real-world observational study based on the SEER (**Surveillance, Epidemiology, and End Results**) database including 8000 patients investigated the survival benefit of PT resection according to metastatic pattern at diagnosis (58). They found that local breast surgery of bone-only metastasis patients offered a significant survival improvement (HR=0.83, $p<0.05$), which was not found for patients with other single-organ locations. Another retrospective study suggested that the subset of patients with bone-only metastases, even when they were multiple, could benefit from LRT (27). **For oligometastatic disease, some retrospective and prospective series demonstrated that local treatment of all metastases, when feasible, was significantly associated with prolonged survival (63). Patients with oligometastatic bone-only MBC treated with stereotactic radiotherapy had better clinical outcomes than other sites of metastases (64). In a study from the SEER database, after stratification based on the distant organ involved, authors found that local breast surgery was**

associated with a better survival in patients with only one distant organ involved (such as bone, liver or lung) excepted for brain-only metastasis (65). This asks the question of the adequate timing for each local treatment (PT and metastases) which is still unknown and should be discussed in multidisciplinary concertation. Two ongoing prospective phase III trials (NCT02089100, NCT02364557) are evaluating the role of metastases local ablation (Stereotactic Body Radiation therapy (SBRT) or surgery) with curative intent in oligometastatic breast cancer. In dnMBC patients, the PT has to have been treated with curative intent. Interestingly, NCT02089100 study excluded patients with TN tumors.

Indeed, one major limitation of the retrospective studies was that IHC profile was not available, although each subtype of BC has a preferential site for metastasis: HR-positive tumors tend to metastasize to bone, whereas both HER2-positive and TN tumors are at high risk of developing visceral and brain metastases (66–68). In addition, each IHC profile has a distinct prognosis with the availability of tailored therapies. Indeed, the survival trend in metastatic patients with HER2-positive tumors treated before the advent of anti-HER2 treatment was similar to that in women with TN tumors (62). Therefore, disregarding the IHC profile and the advent of anti-HER2 therapies when considering LRT induces a severe bias.

Unfortunately, studies focusing on the role of LRT on survival outcomes in the light of IHC profile are limited. The first study was conducted between 2000 and 2004 by Neuman *et al.* but included only 186 patients (31). The authors reported that surgery was not associated with improved OS in patients with TN tumors, whereas it was associated with improved survival in patients with either HR or HER2-positive tumors when hormonal therapy and trastuzumab were used. Results were confirmed in other studies for patients with HER2-positive tumors who received trastuzumab, and for those with HR-positive tumors (60,69,70). In contrast, Dominici *et al.* did not find that surgery improve survival after adjusting for trastuzumab therapy, but patients who had surgery in the earlier time period (1997-2004) could negatively biased the study (49). A recent multicenter French retrospective study involving more than 4000 patients between 2008 and 2014 demonstrated that LRT was associated with a better OS in patients with HR-positive (62 vs 46 months, n=2356) and HER2-positive (77 vs 53 months, n=918) tumors, but not in TN tumors (19 vs 19 months, n=495) (7). In this study, all patients received adapted hormonal and/or targeted therapy (excepted cyclin-dependent kinase 4/6 inhibitors). Interestingly, the IHC subtype along with the efficacy of tailored therapy seemed to impact the benefit of LRT more than the pattern of metastatic dissemination (7). Conversely, a study conducted between 2010 and 2013 on the SEER database and including more than 9000 patients (1311 patients with TN tumors) found

that the survival benefit was similar regardless of IHC, but the median follow-up was very short (only 13 months), so no conclusions could be drawn (57).

To conclude with IHC tumor profiles, without effective tailored ST as is the case for TN tumors, LRT seems to provide no benefit other than for palliative purposes. However, a recent study focused specifically on the impact of PT resection in patients with dnMBC TN tumors (n=1737 from 2010 to 2016) (71). The authors proposed a predictive nomogram based on seven independent risk factors which included demographic features (age and marital status) and clinicopathological variables (T stage and bone/brain/liver/lung metastases). The total score of an individual classified the patient into one of three risk-groups. The conclusion was that surgery could improve survival only in highly selected low- and intermediate-risk groups. Therefore, prospective studies including metastatic dissemination along with tailored adapted systemic therapies taking IHC profile into account are needed to enlighten the debate concerning LRT in dnMBC.

2.4 Lessons learned from prospective studies

In the last four years, three prospective phase III randomized studies have been published, all with OS as primary objective, with divergent results (Table 2). The first trial was a monocenter Indian study conducted between 2005 and 2013 (72). **Patients with single-metastasis amenable to a treatment with a curative intent were excluded.** Patients first received induction ST and only those who responded were next randomized to surgery +/- RT, *vs* no LRT. Importantly, following induction therapy, if response or stable disease was obtained, ST was not maintained but only resumed after progression. This means that if the local treatment accelerated the growth of metastatic lesions (concept of “surgical wounding” described in part 4.2), it was not controlled with additional ST. Moreover, patients did not receive ST according to BC IHC subtypes, so no comparison with current standard of care was possible. The median OS was not improved by LRT (20.5 *vs* 19.2 months between the LRT / no-LRT groups). However, LRT was associated with a significant improvement in locoregional disease control compared to no LRT ($p < 0.0001$).

The two other prospective trials randomized patients before any ST prior to LRT. This time, ST included chemotherapy, anti-HER2 and hormonal therapy according to IHC subtypes. The MF07-01 trial from Turkey (73) suggested a potential benefit after the fifth year of follow-up (41.6% of the patients were alive in the LRT group *vs* 24.4% in the no-LRT group ($p = 0.005$)), that was not observed in a previous report after only 3 years (60% *vs* 51% of survival between both groups, $p = 0.10$). Unplanned subgroup analysis suggested a potential

benefit in patients with an HR-positive, HER2-negative tumor, younger than 55 years, and with a metastatic disease limited to a solitary bone lesion. On the other hand, patients with multiple liver/pulmonary metastases had a significantly worse prognosis with initial surgery. For patients with TN tumors, the median OS was not different between the groups (17.5 vs 18 months in the LRT / no-LRT group). The third study was an Austrian study (POSITIVE, ABCSG 28) that failed to demonstrate any benefit associated with LRT (74). Due to poor recruitment, the study was stopped prematurely (after the inclusion of only 90 patients out of the 254 needed), so the results should be interpreted with caution. Stratification was done according to tumor grade, IHC, visceral vs bone-only metastases, and planned first-line ST. Median OS was 34.6 months in the LRT group vs 54.8 months in the no-LRT group. Time to local progression (including breast and lymph nodes) was similar between both arms (HR=0.93). Post hoc analysis suggested that luminal A patients had worse results after upfront surgery (HR=0.3 (0.1-0.8)). Other subgroups were insignificant. A QoL analysis revealed no difference between both groups.

In conclusion, based on the prospective available studies, different approaches at the time of randomization (before or after primary ST) and different availabilities of modern ST (including targeted therapies), the results are divergent. Therefore, no definitive conclusions can be drawn about the benefits of breast surgery. As testimony to the difficulty of resolving this question, other studies failed to be ended. One randomized trial from the Netherlands was closed in 2014 due to poor enrolment (SUBMIT, NCT01392586), and one from Thailand was withdrawn (NCT01906112).

Fortunately, results from other prospective trials will soon be available (Table 3). In a Japanese Clinical Oncology Group study (JCOG 1017) and an American Eastern Clinical Oncology Group (ECOG 2108) study, after a first line of the most up-to-date ST according to their IHC status, women were randomized to undergo surgery or no (+/-RT). ST were continued (75,76). These two studies have now completed the enrolment. **First results of the phase III ECOG were presented at the ASCO (American Society of Clinical Oncology) congress 2020 and reported no survival benefit of surgery and radiotherapy of the PT, with no differences according to IHC status in terms of OS. Subgroup analysis according to the metastatic site has not been presented yet. Before drawing any proper conclusion, we are waiting for the publication of the study.** A third prospective, non-randomized study should begin soon in France (PALATINE, NCT03870919), evaluating the combination of palbociclib plus letrozole with LRT (surgery +/- RT, or ERT) after six months of ST. This

study is particularly interesting as it also investigates the type of LRT, which is also an important issue.

3. Metastatic breast cancer, a disease where survival and comfort matter: which LRT?

3.1 Surgery: an old candidate

Surgery of the PT in dnMBC has been performed for decades but the preferential type of surgery in this singular context remains unknown. We will not discuss this topic in an exhaustive manner as it is the focus of a specific review (59). We will only address some key points.

First, concerning the type of surgery, few studies have compared the OS benefit between radical treatment and conservative treatment. Whereas studies reported no difference in OS between the two types of surgery, complete excision with clear surgical margins reduced the risk of death significantly (27,38,53,77). In another study, however, OS was better in the mastectomy group, but 26% had positive margins in the lumpectomy group vs only 3% in the case of total mastectomy ($p < 0.001$) (42). Therefore, it seems that if surgery of the PT is considered for dnMBC other than for palliative reasons, it should be planned with the intent of obtaining negative margins (25). To date, the benefit of axillary dissection on survival has not been demonstrated, and it is particularly morbid (78). Therefore, it is to date not indicated but it can be discussed on a multidisciplinary basis, associated with optimal breast surgery, for patients with initial axillary lymph node involvement.

Because it has existed for decades, LRT is often only thought of in terms of surgery. However, only a few studies have investigated the benefit of ERT, yet it is far from lacking value.

3.2 Exclusive RT (ERT): data on overall survival

Only a few studies (summarized in Table 4) have evaluated survival outcome in patients who received ERT (77,79–81). However, it appears that up to 40% of physicians propose it in clinical practice (81). All these studies are retrospective as none of the prospective studies terminated or ongoing (Tables 2 and 3) included an ERT group. The most important limitation is that all studies except one stopped recruiting patients long before new systemic therapeutic advances in MBC became available, especially anti-HER2 targeted therapies. Moreover, they do not give much information concerning the different techniques of RT.

Two studies were monocenter, both recruiting until 2003/2004 (79,80). The first compared an LRT group in which 78% patients received ERT (n=249/320) to a non-LRT group (n=261) (79). The authors demonstrated that LRT was associated with a significantly better OS (HR=0.70 [0.58; 0.85]), and ERT was an independent factor for OS in multivariate analysis. The other monocenter study compared ERT (n=147) with surgery-based LRT (n=92, combined with RT for 70% of them) (80). Results were similar for OS between both modalities (HR=1.05 [0.72; 1.73]), without comparison with a non-LRT group.

Two larger multicenter studies also evaluated ERT. The first one was from the British Columbia Database and was conducted between 1996 and 2005 (77). It was not specifically designed to analyze an ERT group, but rather to compare LRT (n=378) *vs* no-LRT (n=355). However, ERT represented a significant number of patients (22%, n=82), whereas surgery alone and both treatments represented 67% (n=255) and 11% (n=41), respectively. LRT, regardless of the modality, was associated with a significantly better OS in multivariate analysis (HR=0.78 [0.64; 0.94]). Finally, the most recent and largest multicenter study was conducted between 2008 and 2014 and included 1965 patients from 18 French Cancer Centers (81). The impact of each LRT modality on OS was analyzed separately compared to a no-LRT group: 366 patients (41%) underwent exclusive RT, 122 (14%) exclusive surgery and 403 (45%) a combination of both. To limit the selection bias described above, only patients free from progression at least one year after diagnosis were included. After adjustment on confounding factors, ERT was significantly associated with a 37% reduction in the risk of death (HR=0.63 [0.49, 0.80]), in the same range as surgery associated with RT (39%, HR=0.61 [0.47, 0.78]) compared to no-LRT (81).

Reasons for the choice of the type of LRT were probably associated strongly with the clinical context, which is not specified in retrospective studies. Patients who received ERT *vs* surgery-based treatment had larger PT size and a greater tumor burden (80,81). Regarding IHC, TN and HER2-positive tumors were more often treated with ERT, whereas HR+/HER2-negative tumors more often received a combined therapy with surgery plus RT (81). It seems that patients with more indolent diseases (luminal) are more likely to benefit from a "complete" LRT.

3.3 Exclusive RT: a credible alternative to surgery for locoregional control?

The literature is sparse regarding ERT as an alternative to breast surgery for locoregional control, but there is some proof that it could be an effective means of control in selected patients. It has been studied mostly in localized disease, for elderly people who are often

associated with disabling disease, making oncologists or the patients themselves reluctant for surgery. For example, hypofractionated RT (which is not the current standard) was analyzed in 115 elderly non-metastatic patients (after 3-6 months of hormonal therapy for HR+ patients) (82). The 5-year local PFS was 78% (included 33% \geq T3). Local failure was not correlated with tumor size or nodal status. Chargari *et al.* (83) studied 29 patients with localized T1-T2 invasive tumors, N0 for 62% of them, who received ERT (32.5 Gy/5 fractions/5 weeks followed by a 13 Gy boost) concomitantly to hormonal therapy. With a median 7-year follow-up, locoregional control was 95.8% and cause-specific survival was 96.4%.

The retrospective studies listed in Table 4 provide additional information regarding local disease control with ERT in dnMBC. RT doses and fields, when available, are described in the table. Bourgier *et al.* (80) found that only 8/147 (5.4%) patients developed a local recurrence after a median follow-up of 6.5 years [1-15.4]. In the Canadian study (77), patients who received LRT (but only 22% received ERT) had significantly improved locoregional PFS compared to no-LRT patients, from 46% to 72% at 5 years ($p < 0.001$). Another study, without a comparative arm, found a local PFS at 5 years of 67.3%, but half of the patients (67/125) also received surgery plus RT (84). The French multicenter study found a significant decrease in the risk of progression compared to no-LRT: 31% for ERT (HR=0.69 [0.59; 0.81]) and 35% for combined modalities (HR=0.65 [0.55; 0.76]) (81). However, they did not differentiate local and distant progression, so it was impossible to draw any firm conclusions.

3.4 Surgery, radiotherapy, or both: is it ethical to risk toxicity without evidence of efficacy?

Optimal management of dnMBC should maintain the highest QoL for patients since the disease is incurable (25). However, breast conservative surgery, mastectomy, axillary dissection, RT, and sometimes the combination of all these modalities may alter the image of the body and require hospitalization, anesthesia, and several trips back to the hospital. In addition, there are few data in the literature regarding the efficacy of LRT, and even less regarding its toxicity. Surgery could lead to complications such as hematoma, lymphedema, and infection. Moreover, questions arise about breast reconstruction after mastectomy, which could increase the risk of surgical complications (85). Nor is RT without side-effects, such as early skin reactions and esophageal toxicities, or later ones such as subcutaneous fibrosis, telangiectasia, and lymphedema. The combination of ST and RT may cause cumulative side-effects, especially cardiotoxic effects or pulmonary fibrosis. On the other hand, QoL may also be impaired by an uncontrolled chest wall, thereby justifying medical procedures (14).

Moreover, palpation of a residual tumor may result in high anxiety, altering QoL, and inviting patients themselves to ask for removal of the PT to feel better.

ERT may offer satisfactory local control, without undergoing surgery. In addition, RT can be performed on an outpatient basis, without the need for anesthesia or a surgical block, which can be important in older or frail patients. A recent observational study evaluated the feasibility and the toxicity of helical tomotherapy to control locoregional tumors in dnMBC and locally advanced BC (86). 39% had undergone surgery before RT, and ST was administered concurrently in 91% of cases. RT led to significant clinical improvement in 75% of cases with tumor involving skin (n=19 patients), with a positive impact on QoL. In seven of eight patients with locally advanced tumors, there was tumor regression. At the other hand, these series have shown that patients treated for metastatic disease who responded to ST had better OS after locoregional RT, in comparison with those who were presented with locally advanced BC without metastasis, but who were bad responders to ST (86).

Moreover, whatever the LRT, it should not result in delayed administration of ST, which remains the mainstay of treatment for metastatic disease. Interestingly, for HER2-positive patients, the combination of anti-HER2 therapies along with radiotherapy shows no serious adverse events (87,88). Similarly, for HR-positive patients, CDK4/6 inhibitors in association with radiotherapy also seem well tolerated, as suggested by the latest studies (89,90). However, although neutropenia is rapidly reversible, it is nonetheless the most frequent adverse event reported with these therapies so the risk of infection should be borne in mind, especially after surgery.

4. What evidence do we have from benchside research?

Since cancer cells in dnMBC disease have already disseminated throughout the systemic circulation and colonized distant organs, researchers have explored the rationale for PT resection. So far, knowledge regarding interactions between the PT and metastatic sites is very limited. We have synthesized the biological hypothesis that could explain the pro and cons of the systemic effect of a local treatment (Fig 1.).

4.1 Tumor debulking

It has been suggested that the PT is not a homogeneous mass of cells. Rather, some PT cells with a major genomic instability might undergo a clonal progression and mutate, thereby becoming more aggressive and more likely to induce metastases (22). The rationale for surgery is to reduce not only the global tumor burden to increase the efficacy of ST but also

the source of tumor stem cells with enhanced metastatic potential. This tumor debulking strategy has been demonstrated in various solid tumors (renal, colorectal, ovarian and gastric). Indeed, the metastatic process has been described as a multidirectional process called “tumor self-seeding” whereby cancer cells from the PT can colonize distant sites as well as their primary site of origin (92,93). It is easy to picture tumor cells preferentially seeding their primary mass of origin, as all the tissue-specific factors that allowed their growth in the first place are concentrated there. However, self-seeding selects for highly aggressive tumor cells, as they have undergone selection for movement into and survival in the circulation. Therefore, PT may foster the expansion of potentially very aggressive metastatic progenies (94). Tumor self-seeding by circulating tumor cells (CTC) enhances tumor progression and metastatic dissemination. Three of the ongoing prospective studies cited above (ECOG, JCOG and MSKCC trial) are currently evaluating CTC burden between a surgery and a non-surgery group, and whether PT resection influences the number of CTC and correlates with survival. Lastly, tumor debulking by surgery or radiotherapy reduces the systemic immunosuppressive activity of malignant cells, as discussed in part 4.3.

4.2 Surgical wounding

Surgical wounding after tumor resection can trigger the outgrowth of tumors at distant anatomical sites and contribute to escape from dormancy. This was first suggested by Fisher *et al.* 30 years ago when they hypothesized that PT resection may promote the progression of distant metastases by the secretion of growth-stimulating factors (95). Much more recently, Krall *et al.* demonstrated in a mouse model that surgical wounding induced the release of cytokines and an elevation of the myeloid cell population in the circulation, which could break immune-imposed dormancy and enable tumor outgrowth of dormant metastases (96,97). Moreover, wound repair following breast surgery could stimulate residual neoplastic cells to acquire the tools for epithelial-to-mesenchymal transition, thus promoting dissemination. Concordant with these pre-clinical data, early BC patients whose tumors expressed a wound-response gene expression signature had worse OS and metastasis-free survival than those with tumors that did not (98). Thus, if surgical wounding has potential negative effects, one potential benefit of exclusive RT would be to avoid it.

A retrospective clinical study analyzed the relationship between wound complications occurring after surgery of a primary BC and the development of systemic recurrence. Patients who had wound complications, defined as any wound breakdown that needed surgical debridement, dressing or packing, had a significantly greater risk of developing systemic

recurrence (HR=2.52 [1.69; 3.77] (97). Interestingly, the TATA Memorial's prospective study (part 2.4) concluded that surgical LRT was associated with a significant detriment in distant PFS compared to no-LRT (11.3 vs 19.8 months) (72). As a reminder, further ST was not administered after LRT in that trial. Similarly, the POSYTIVE trial identified a trend towards worse results for luminal A patients after upfront surgery. However, these results should be interpreted carefully because numerous biases were present in the TATA trial, and the POSYTIVE trial was stopped prematurely (part 2.4).

4.3 Potentiate anti-tumoral immune response

Another major argument to treat the PT comes from the relationship between the immune system and the PT. Experimental studies evaluated the impact of PT resection on metastatic sites, and especially on global immunosuppression. It was demonstrated in a murine model with transplantable tumors that immunosuppression is reversed following PT removal, by comparing immune responses in mice with intact PT vs mice whose PTs have been removed but which had established metastatic disease. Interestingly, the presence of PT suppresses T-cell and antibody responses (99). Another study concluded likewise by demonstrating with fibrosarcoma cells that PT resection unmasked a population of primed T cells able to mediate protective immunity (100).

RT has also demonstrated effects on systemic immune response, and particularly on tumor-induced immunosuppression (101). Thus, the use of RT on tumor cells to boost anti-tumor response is attractive. Accumulated evidence showed that besides a direct cytotoxic effect, ionizing RT is a powerful inducer of apoptosis in tumor cells, and induces a specific death modality called "immunogenic cell death" (102,103). Therefore, it can enhance the release of "danger" signals, and thus promote anti-tumor T cell priming. It could also facilitate the penetration of antigen-presenting cells and effector T cells into tumors (99,104,105). Another immune-related RT is called the abscopal effect, i.e. the reduction of the tumor growth by RT outside the field of radiation (105–107), owing to local activation of systemic antitumor immunity. This concept has been demonstrated in pre-clinical mice transplanted models, where the irradiation of one tumor site resulted in tumor growth inhibition at the other non-irradiated site (99,105). In dnMBC, a case report described a patient with a high tumor burden who presented a dramatic regression of metastatic lesions after an exclusive treatment with RT (of the PT and some of the bone metastases) (108). However, in view of numerous disappointing studies, the abscopal effect is the subject of much debate (104,109).

Because we are on the cusp of a new therapeutic era in solid oncology with immune checkpoint inhibitors (ICI), especially in TN subtypes for MBC patients (17), pre-clinical studies have combined RT with ICI, and several clinical studies are ongoing (reviewed in (104)). It was demonstrated in a poorly immunogenic transplantation mouse model that when RT of the PT in metastatic breast disease was combined with ICI, CD8+ T-cell-dependent antitumor immunity was elicited and it inhibited the growth of metastases (99). However, when taken individually, each treatment was ineffective: RT alone to the PT significantly delayed the growth of the primary irradiated tumor but had no impact on survival rate. RT increased tumor-infiltrating lymphocytes CD8+ and expanded the TCR repertoire of T cells, whereas ICI narrowed it and drove the expansion of a limited number of clones. This therefore explained why the combination of RT and ICI could induce metastatic tumor rejection, by the clonal expansion of specific tumor T-cell clones (110). Importantly, most pre-clinical studies used injected subcutaneous tumor mouse models (99,105,111), which is far removed from the clinical situation of a dnMBC patient.

5. Conclusion

In the era of modern systemic and locoregional therapies, the question of LRT in dnMBC is a multidisciplinary challenge involving surgeons, radiation oncologists, medical oncologists and the patients themselves. To date, guidelines have suggested that the removal of the PT could be considered only in highly selected patients, as it has not been associated with a high level of evidence that it increases survival significantly (25). **Age should not be a limitation, provided that global health status and life expectancy is not limited by another pathology.** The biology of the disease, the pattern of metastatic disease and sensitivity to first-line ST could thus help in proposing the best loco-therapeutic option, although the type, order and timing of treatments are left to the multidisciplinary team's judgment. However, one should recall that the goal of care in the metastatic setting should always be to maintain the highest QoL while optimizing disease control and that discussion with the patient about the risk/benefit balance is crucial.

LRT should be discussed after checking that ST controls metastatic disease, except in cases where its objective is to control palliative symptoms. Here are three clinical situations that could occur after first-line ST (Graph. Abstract):

- First resistance to ST and metastatic disease evolution. In this case, priority should be given to systemic control and LRT should be considered only if the PT becomes symptomatic.

- Both local and distant sites are well controlled, with or without complete clinical response in the breast and other organs. LRT could be proposed, especially in HER2-positive and HR-positive/HER2-negative patients, where there has been dramatic improvement in PFS and OS with the latest targeted therapies. The LRT modalities need to be discussed by clinicians and patients: ERT, surgery, or a combination of surgery plus RT could be proposed.
- Both local and distant sites are well controlled, with a complete resectable metastatic disease. This situation, known as oligometastatic disease, has emerged as a recent concept (26). If available, inclusions in clinical trials should be proposed. **Two prospective phase III trials (NCT02089100, NCT02364557) are currently enrolling patients and will help us determine the best strategy in this situation. In the meantime, guidelines recommend considering a multimodal approach including optimal LRT of the PT and metastatic sites with curative intent for these patients (25).**

When available, clinical trial addressing the value of LRT, the best candidates and best timing should be proposed.

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Tables and figures

Table 1: Observational studies comparing LRT (surgery +/- radiotherapy) with no-LRT in dnMBC patients, classified by years of recruitment.

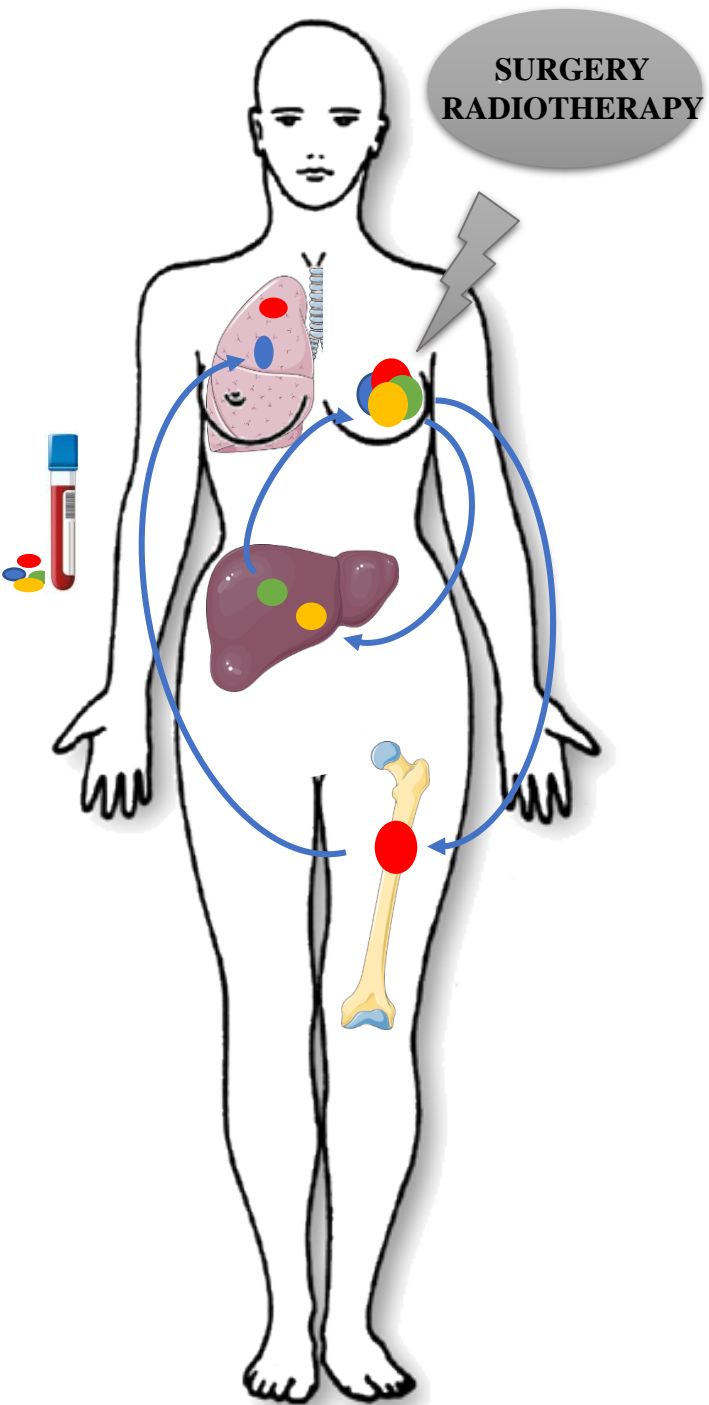
Table 2: Prospective completed randomized trials which evaluated efficacy on overall survival of primary tumor resection in dnMBC.

Table 4: On-going prospective trials evaluating locoregional treatment in dnMBC.

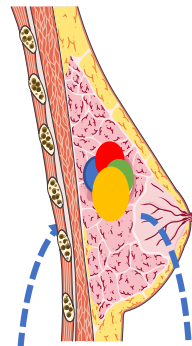
Table 3: Retrospective studies evaluating exclusive radiation therapy as locoregional treatment in dnMBC.

Figure 1: Biological effects of loco-regional treatment in dnMBC.

Graphical abstract: Decision algorithm to select the optimal candidates for LRT in dnMBC.



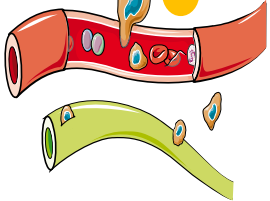
Loco-regional effects



- ↓ Tumor burden
- ↓ The source of aggressive tumor cells'
- ↓ Cancer stem cells
- ↓ Of clonal heterogeneity

- ↑ Cell growth at the wound site

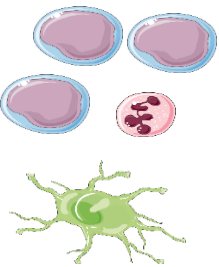
Invasion



- Disruption of crosstalk between primary tumor and metastases
- ↓ Primary-derived circulating tumor cells and disseminated tumor cells
- ↓ Circulating tumor-derived factors that prime metastatic niche

- ↑ Pro-angiogenic effects
- ↑ Epithelial-mesenchymal transition for residual tumor cells
- ↑ Cell mobility

Immune effects



- Restore immunocompetence
- Induce immunogenic cell death
- Promote infiltration by T cells
- Abscopal effect

- ↑ Immunosuppressive cytokines and cells

Table 1: Observational studies comparing LRT (surgery +/- radiotherapy) with no-LRT in dnMBC patients, classified by years of recruitment.

Study	No. of patients	Selection period	Patients with single-organ metastases (%)	Patients with visceral metastases* (%)	Patients who underwent LRT (%)	Median OS (months)		Hazard ratio OS	P value
						LRT	No LRT		
Cady Ann. Surg. Oncol 2008	622	1970-2002	NA	NA	38	31	20	NA	<.0001
Blanchard Ann. Surg. 2008	395	1973-1991	68.4	50.4	61.3	27.1	16.8	0.71	.006
Rapiti J. Clin. Oncol. 2006	300	1977-1996	49	52	42	NA	NA	0.6 (free margins)	.049
Perez-Fidalgo The Breast 2011	208	1982-2005	59.6	51.9	59.1	40.4	24.3	0.52	.001
Gnerlich Ann. Surg. Oncol. 2007	9 734	1988-2003	NA	NA	47	36	21	0.63	<.001
Thomas JAMA Surg. 2016	21 372	1988-2011	NA	NA	39	28	19	0.6	<.001
Vohra Breast J. 2018	29 916	1988-2011	NA	NA	49.4	34	18	NA	<.0001
Khan Surgery 2002	16 023	1990-1993	63.9	38.8	57.2	25.3 (free margins)	11.9	0.61 (free margins)	NA
Yoo Breast Cancer Res Treat 2017	2 232	1990-2014	NA	NA	69	53	31	NA	<.001
Kolben Breast Care 2016	236	1990-2006	58.9	57.2	83.1	28.9	23.9	0.63	<.001
Leung J. Surg. Res. 2010	157	1990-2000	37 (bone-only)	63	33	25	13	NA	.36
Mc Guire Am. J. Surg. 2009	566	1990-2007	NA	52.9	27.4	48.6	27.4	NA	.012
Lopez- Tarruella Sci. Rep. 2019	1 331	1990-2001	49.2	48.3	44.5	39.6	22.4	0.685	<.001
Ruiterkamp Eur. J. Surg.	728	1993-2004	63.4	57.4	40	31	14	0.62	<.0001

Oncol. 2009										
Pathy Br. J. Surg. 2011	375	1993-2008	55.2	NA	37.1	21.3	10.1	0.72	<.001	
Hazard Cancer 2008	111	1995-2005	62	62	42	26.3	29.3	0.8	.5	
Ruiterkamp Breast Cancer Res. Treat. 2011	8 031	1995-2008	NA	NA	23-31	31	15	0.64	<.0001	
Rhu ANZ J. Surg. 2015	262	1995-2011	56.5	NA	15.3	NA	NA	0.51	<0.01	
Fields Ann. Surg. Oncol. 2007	409	1996-2005	26.9	NA	46	26.8	12.6	0.53	<.0001	
Babiera Ann. Surg. Oncol. 2006	224	1997-2002	76	57	37	NA	NA	0.50	.12	
Dominici Breast Cancer Res. Treat. 2011	290	1997-2007	53	NA	19	42	41	0.94	.27	
Bafford Breast Cancer Res. Treat.2009	147	1998-2005	NA	NA	41	42	28	0.47	.003	
Warschkow Ann. Surg. 2016	16 247	1998-2009	NA	NA	47	NA	NA	0.53	<.001	
Xie Medecine 2017	223	1999-2014	NA	NA	79.4	45.6	21.3	0.57	.044	
Neuman Cancer 2010	186	2000-2004	13 (solitary metastasis)	60	37	40	33	0.71	.1	
Barinoff Eur. J. Cancer 2017	568	2000-2011	NA	77	75	34.1	31.7	0.95	.71	
Lane Ann. Surg. 2019	24 015	2003-2011	13 (bone-only)	86.7	43.8	After systemic treatment:52.8 Before: 49.4	37.5	A: 0.56 B: 0.68	<.001	
Arciero Breast J. 2019	11 674	2004-2013	NA	NA	44.5	51.8	38.1	0.68	<.001	
Kommalapati Breast Cancer Res. Treat.2018	67 978	2004-2015	81	NA	34	45	24	NA	<.0001	
Xiong BMC Cancer	313	2006-2013	NA	53.4	60.1	78	37	0.53	.001	

2018										
Choi Clin. Breast Cancer 2018	245	2006-2013	NA	NA	29.8	NA	NA	0.62	.26	
Quinn Breast 2015	109	2006-2012	63.3	60.6	47.7	35.8	20.2	NA	.013	
Pons-Tostivint Ann. Surg. Oncol. 2019	4 276	2008-2014	50.8	52.7	40	NA	NA	0.51	<.001	
Wu Oncotarget 2017	9 256	2010-2013	NA	NA	33.8	44	23	0.46	<.001	
Wang Eur. J. Surg. Oncol. 2019	8 142	2010-2015	60.8	NA	23	3-year OS 54.4	3-year OS 47.7	0.82	<.001	

Abbreviations: LRT=locoregional treatment; NA=not available; dnMBC=de novo metastatic breast cancer; OS=overall survival.

*: Some studies included distant nodes and metastases to the central nervous system in visceral metastases and are reported indistinctively in our table. Other studies detailed the percentage of patients metastatic for each organ but did not specify the overlap of metastatic organs not enabling us to calculate the total percentage of patients with visceral metastases (marked as NA in our table).

Table 2: Prospective completed randomized trials which evaluated efficacy on overall survival of primary tumor resection in dnMBC.

Study	Accrual period	No. Patients	Primary endpoint	Initial therapy	Subset analyses	Loco-regional treatment modalities	Hazard ratio for OS (95% CI)
TATA Memorial Badwe [48]	2005-2013	350	OS	Systemic therapy	Age, ER, HER2, number and type of M+	BCS or mastectomy including axillary staging +/- RT	1.04 (0.8-1.3)
MF07-01 Soran [49]	2007-2012	274	OS	Surgery	Unplanned: ER, HER2, age, type of M+	BCS or mastectomy including axillary staging +/- RT	0.66 (0.49-0.88)
ABCSG 28 Fitzal [50]	2010-2015	254 pre-planned 90 randomized	OS	Surgery	ER, HER2 status, grading, first line chemotherapy, metastatic site	BCS or mastectomy including axillary staging +/- RT	HR for no-LRT 0.69 (0.36-1.33)

Abbreviations: dnMBC= de novo metastatic breast cancer; OS= overall survival; ER=estrogen receptor; HER2=human epidermal growth factor 2; BCS=breast conservative surgery; RT=radiation therapy; M+=metastasis.

Table 3: On-going prospective trials evaluating locoregional treatment in dnMBC.

Study	Status	Location	No. Patients estimated / actual	Primary endpoint	Type of study	Stratification	Loco-regional treatment
MSKCC NCT00941759	2009-2020 Active, not recruiting	USA	100	Response to first-line therapy, frequency of surgical referral and proportion of patients who undergo surgery	Observational	No	Surgery
ECOG 2108 NCT01242800	Beginning 2011	USA	880/391	OS	RCT Within 16-32 weeks after start of systemic therapy, with stable disease or response: systemic therapy alone or LRT + systemic therapy	HR, HER2, systemic therapy, metastatic sites	BCS or mastectomy with free surgical margins +/- RT
JCOG 1017 PRIM-BC UMIN000005586	Beginning 2011 Accrual period completed 2018	Japan	600/410	OS	RCT No progressive disease with first systemic therapy: systemic therapy alone or LRT + systemic therapy	No	Surgery
PALATINE NCT03870919	Not yet recruiting	France	200 HR+ patients.	OS	No randomization. LRT will be proposed after 6 courses of Palbociclib + Letrozole. Only HR+ patients.	No	Surgery +/- RT Exclusive RT
BOMET MF 14-01 NCT02125630	Recruiting 2012-2018	Turkey	250 Only bone metastasis patients	OS	RCT Primary surgery versus exclusive systemic therapy	No	Surgery

Abbreviations: RCT = randomized controlled trials; OS = overall survival; LRT = locoregional treatment; HR = hormonal receptor; BCS = breast conservative surgery; RT = radiation therapy

Table 4: Retrospective studies evaluating exclusive radiation therapy as loco-regional treatment in dnMBC.

Study	Accrual period	Institution	Groups	Type of LRT (No. patient)			No-LRT (No. patients)	RT doses and fields	Hazard Ratio OS	Loco-regional control
				Exclusive RT	Surgery + RT	Exclusive Surgery				
Le Scodan 2009 [58]	1984-2004	France, monocenter	LRT vs no-LRT	249	41	30	261	<i>Exclusive RT:</i> Mean 48.7 Gy to the breast and 48.0 Gy to the axillary and supraclavicular LN. 63.5% received tumor boost. 42.7% axillary LN. 20% supraclavicular LN.	HR=0.70 [0.58; 0.85] p=0.0002	NA
Bourgier 2010 [59]	1990-2003	France, monocenter	Exclusive RT vs Surgery +/- RT	147	64	28	not included	<i>Exclusive RT:</i> 50 Gy / 25 fractions for 32% of patients. 30 Gy / 10 fractions for 63% of patients. 59-74% received tumor boost. 70-83% axillary LN. 75-89% supraclavicular LN.	HR=1.05 [0.72; 1.73] p=0.82	Exclusive RT: 55% clinical complete response
Nguyen 2012 [53]	1996-2005	Canada, multicenter, British Columbia Database	LRT vs no-LRT	82	41	255	355	<i>All RT:</i> 40-50 Gy. 62.6% breast plus LN. 26% Breast alone. 9.8% Chest wall plus LN. 1.6% chest wall alone.	HR=0.78 [0.64; 0.94] p=0.009	5-year LR PFS 72% vs 46% LRT / no-LRT
Mauro 2016 [63]	2005-2013	Brazil, monocenter	RT-based therapy No comparative arm	58	67	not included	not included	All RT: 50 Gy / 25 fractions for 36.3% of patients. 40 Gy / 15 fractions for 22.8% of patients. 8-30 Gy / 1-10 fractions for 40.9% of patients. 90.6% breast / chest wall. 54.3% LN.	Not available	5-year LR PFS 67.3%
Pons-Tostivint 2020 [60]	2008-2014	France, multicenter, ESME Database	Each LRT vs no-LRT	366	403	122	1074	NA	HR=0.63 [0.49,0.80] (Exclusive RT vs no-LRT) P=<0.001	NA

Abbreviations: LRT=locoregional treatment; NA=not available; dnMBC=de novo metastatic breast cancer; OS=overall survival; RT=radiation therapy; LN=lymph nodes; Gy=grays.