Aggressive local therapy for *de novo* metastatic breast cancer: Challenges and updates (Review)

BAILONG LIU*, HUI LIU* and MIN LIU

Department of Oncology, The Second Affiliated Hospital of Anhui Medical University, Hefei, Anhui 230601, P.R. China

Received January 13, 2023; Accepted June 28, 2023

DOI: 10.3892/or.2023.8600

Abstract. Systemic therapy has been viewed as the mainstay for *de novo* metastatic breast cancer (dnMBC). However, as dnMBC is highly heterogeneous both biologically and clinically, and with ever-improving systemic strategies, it has been implied that the local therapy of the primary tumor (PT) may be beneficial for certain patients with dnMBC. However, the results from retrospective studies have been questioned due to their selection bias and retrospective nature. To the best of our knowledge, there are two published randomized clinical trials addressing this issue with conflicting conclusions: i) TATA study from India indicated no overall survival (OS) superiority with early local radiotherapy (LRT); and ii) MF07-01 indicated a 5-year OS rate improvement of 17% with upfront LRT. The updated results of a randomized phase III ECOG-ACRIN E2108 trial released in the 2020 American Society of Clinical Oncology (ASCO) meeting reported a negative survival effect of early LRT treatment in patients with dnMBC responding to initial systemic treatment, despite LRT significantly reducing the locoregional failure. Thus, a number of issues, such as the exact value of LRT, the optimal means of LRT (surgery and/or RT to the PT), the ideal timing of LRT and the population most likely to benefit from LRT, warrant further investigation. Herein, the related studies focusing on these aspects were comprehensively reviewed and a decision algorithm was proposed to select suitable patients with dnMBC for reasonable LRT. Generally, upfront systemic therapy is recommended. For good respondents and a subgroup of favorable profiles (young age, good general condition, low tumor burden, hormone receptor-positive and so on), radical LRT including PT surgery followed by RT and the resection of distant metastases is recommended. LRT should also be administered if the PT is still symptomatic. LRT may benefit patients with dnMBC due to the following reasons: Control of the PT decreases tumor burden, eliminates the source of dissemination, enhances the sensitivity to therapy and exerts positive immunomodulation. Therefore, the treatment paradigm for dnMBC may change from 'palliative LRT' into 'curative LRT' in a highly selected entity with careful evaluation.

Correspondence to: Dr Min Liu, Department of Oncology, The Second Affiliated Hospital of Anhui Medical University, 678 Furong Road, Hefei, Anhui 230601, P.R. China
E-mail: liumin05162022@126.com

*Contributed equally

Key words: de novo metastatic breast cancer, local therapy, surgery, radiotherapy, beneficiary

Contents

1. Introduction

De novo metastatic breast cancer (dnMBC), namely MBC at the initial diagnosis, comprises 5-10% of all newly diagnosed breast cancer cases worldwide (1-4). Compared with recurrent MBC, dnMBC is associated with a notably improved 5-year disease specific survival (DSS) rate (44 vs. 21%) and an improved 5-year DSS over time (55% in 2005-2010 vs. 28% in 1990-1998) (5). With the improvement of diagnostic and intervention methods in the field of breast cancer, the median overall survival (OS) of patients with dnMBC has also improved over time (6). The 3-year OS rate of patients with dnMBC increased from 38.7% in the 1990s to 70.1% in 2010-2014 in candidates diagnosed in Korea (7). The 10-year OS rate has been shown to be ~13% (4).

Historically, dnMBC was regarded as incurable and systemic strategy remained the cornerstone of treatment. Local treatment of the primary tumor (PT) has been reserved as a palliative treatment to control symptoms, such as skin ulcerations, bleeding and pain (8). However, an emerging collection of retrospective studies determined that complete PT removal was beneficial for the survival of patients with dnMBC (3,7-13). Bhoo-Pathy *et al* (14) revealed that in an Asian setting, a higher proportion of patients with dnMBC underwent PT surgery with

free margins in recent years. Data from Europe and the USA have indicated that ~40% of patients with dnMBC underwent local radiotherapy (LRT) (2,8,15,16). These findings have been questioned due to study limitations, such as selection bias, stage migration and the retrospective nature. Previous prospective trials have provided conflicting results (17-19). The negative findings presented in certain prospective trials may be the result of the underuse of systemic therapy according to current principles (19). A number of meta-analyses have indicated that surgical excision of the PT leads to a survival advantage in the dnMBC population (20-23). A recent meta-analysis, including 42 studies and 216,066 patients with dnMBC, documented that all forms of LRT reduced the mortality rate by 31.8% (24). Modern systemic therapy strategies grant patients with dnMBC a longer survival and an improved control of metastatic lesions, which encourages clinicians to explore the use of LRT in the treatment of dnMBC (25,26). The present review aimed to identify the optimal means and timing of LRT for the treatment of dnMBC and the population most likely to benefit from LRT, thus providing an important reference for clinical practice.

2. Heterogeneity of dnMBC

dnMBC is highly heterogeneous. This heterogeneity is manifested in different molecular types, gene signatures, metastatic patterns and demographic variables, and these factors interrelate, leading to different outcomes between individuals (27). In a previous study on 7,986 patients with dnMBC from the SEER database from the years 2010-2016, hormone receptor (HR)$^+$/human epidermal growth factor (HER)2$^-$ was the most common subtype (57.6%), followed by HR$^+$/HER2$^+$ (19.0%), triple-negative breast cancer (TNBC; 13.6%) and HR$^-$/HER2$^+$ (9.8%) (27). In addition, 50.3% of dnMBC tumors were poorly differentiated or undifferentiated (27). The prognosis of patients with *de novo* invasive lobular carcinoma may be worse than that of those with *de novo* invasive ductal carcinoma (28). The majority of patients with dnMBC suffer from regional lymph node metastasis, suggesting that regional involvement may precede distant metastasis (29). The most common distant metastatic site is bone, accounting for 73.4% of sites, while the brain is the least common disseminated organ (6.9%) (27). Different subtypes of dnMBC demonstrate specific predilection in distant metastasis. A previous study demonstrated that luminal tumors were more likely to metastasize to bone [P=0.02; bone vs. other organs, including the liver, lungs and central nervous system (CNS)] (30). The upregulated HER2 subtype harbored a liver-homing feature (P=0.0004; liver vs. other sites), while TNBC subtypes were inclined to metastasize to the lungs (P=0.01; lung vs. other sites) (30).

dnMBC differs from relapsed breast cancer (31). During adjuvant systemic treatment, more treatment-resistant tumor clones develop, resulting in disease progression. Therefore, refractory MBC generally harbors a more dismal prognosis than dnMBC (27,32-36). Following active treatment, some patients with dnMBC can obtain a long survival time (37).

Clinicopathologic parameters defining the prognosis of patients with dnMBC. The Epidemio-Strategy-Medical-Economical (ESME)-MBC data platform (NCT03275311) included 16,702 patients with dnMBC from January 1, 2008 to December 31, 2014 (38). Of these patients, the median OS rates of patients with the HR$^+$/HER2$^-$ (n=9,907), HER2$^+$ (n=2,861) and TNBC (n=2,317) subtypes were 42.12, 44.91 and 14.52 months, respectively. Elbaiomy *et al* (39) found that the TNBC subtype of dnMBC highly expressed breast cancer stem cell (BCSC) markers (CD44$^+$ and CD24$^-$), which predicted a poor treatment response, and shorter OS and progression-free survival (PFS) times. In the future, BCSC marker expression may be used to tailor the treatment strategy for patients with dnMBC, and BCSC target therapy may be a promising strategy (39). Dawood *et al* (40) reported that the number of patients with dnMBC surviving >2 years increased over time. A younger age, lower tumor grade, HR positivity, non-inflammatory disease and definitive primary resection contributed to this trend. As previously demonstrated, compared with patients with dnMBC aged 40-59 years, those aged <40 years had a longer survival time, particularly those with the TNBC subtype (41). An uninsured status and older age have also been shown to be associated with early mortality in patients with dnMBC (42). Immediate breast reconstruction has also been shown to not affect survival outcomes when compared with mastectomy in patients with dnMBC (43). In 2002, Khan *et al* (44) performed a comprehensive retrospective study of 16,023 patients with dnMBC in the duration of 1990-1993 using the National Cancer Database. Their findings revealed that four parameters determined the prognosis of patients with dnMBC, including surgical removal of the PT, the administration of systemic treatment, metastatic burden and tumor type (visceral or soft tissue). The retrospective study by Soares *et al* (45) demonstrated that breast surgery (hazard ratio, 0.45) and initial CNS metastasis (hazard ratio, 3.09) were independent prognostic factors for patients with dnMBC. In 2006, Babiera *et al* (11) analyzed 224 patients with dnMBC and revealed that only one metastatic site and no HER2 gene amplification indicated a more favorable OS, while estrogen receptor (ER) positivity and PT resection were closely linked to an improved metastatic PFS (MPFS). Similarly, a previous multivariate analysis of prognostic factors and OS in 395 dnMBC cohorts performed by Blanchard *et al* (46) found that definitive primary surgery, HR positivity and a low number of metastases were associated with an improved prognosis. King *et al* (47) re-evaluated the data of dnMBC cohorts enrolled in the Translational Breast Cancer Research Consortium (TBCRC) 013 program and screened out 101 patients with 21-gene recurrence score (RS) results. In the ER$^+$/HER2$^-$ (n=69) subgroup, a 21-gene low risk (RS <18) score was a strong indicator of an improved 2-year OS and time to first progression (47). The metastatic pattern has a profound impact on the prognosis of patients with dnMBC. The OS times of visceral, nodal and bone-only metastases are approximately <6 months, 18 months and 3-4 years, respectively (48). Lin *et al* (49) determined that the allocation and number of metastatic sites were independent prognostic factors for dnMBC. Therefore, they proposed the subdivision of the M1 stage criteria in a heterogeneous setting: i) M1a, a single metastatic site excluding the liver and brain; ii) M1b, multiple metastatic sites excluding the liver and brain, or liver only involvement; and iii) M1c, liver plus other metastatic sites, or brain only involvement. The M1a subtype benefited

the most from PT resection, while the upstaging of M1 was related to a higher benefit from chemotherapy alone (49). In 2020, Plichta *et al* (50) proposed a novel dnMBC staging system for prognosis. The proposed recursive partitioning analysis including anatomical and biological factors to refine prognostic estimates. The distant metastatic site number and ER status were identified as the first and second stratification points, respectively, and the HER2 status, clinical T stage and tumor grade were incorporated for further divisions. Subsequently, dnMBC was classified into three stages: IVA, IVB and IVC, with a 3-year OS rate of >50, 30-50 and <30%, respectively (50).

Genomic mutations in dnMBC. The genomic analysis of dnMBC was previously conducted to reveal the drivers contributing to the early onset of metastasis (51). In $HR^+/HER2^-$ dnMBC, *PIK3CA* mutations were enriched (41.9%), indicating that PI3K inhibitors may play a critical role in the treatment of this subset. Additionally, *KMTD2* and *SETD2* mutations were more common, while *TP53* and *BRCA1* were less common in $HR^+/HER2^-$ dnMBC, compared with recurrent MBC. In TNBC dnMBC, *MYB* amplification was prevalent and high tumor mutation burden predicted a better prognosis (51). PTEN mutations were more frequent in dnMBC, which are closely associated with immune evasion (52). As previously demosntrated, 11.8% of patients with dnMBC harbored a *BRCA2* mutation, indicating that *BRCA* germline testing was necessary (53).

In dnMBC, with the aim of optimizing disease monitoring, active image evaluation, such as positron emission tomography-computed tomography scanning and magnetic resonance imaging, for CNS screening and tumor marker surveillance is encouraged (54).

3. Timing of LRT for dnMBC

Initial LRT for dnMBC. Thomas *et al* (2) conducted the largest retrospective study of dnMBC (n=21,372) using the SEER database spanning 24 years (1988-2011). Patients undergoing surgery as initial therapy (n=8,330) harbored a significantly longer median OS time than those who did not (n=13,042) (28 vs. 19 months) (2). Additionally, MF 07-01, the first randomized trial, also verified the OS benefit gained by upfront LRT in dnMBC (17). A total of 274 candidates were randomized into two groups: The upfront LRT followed by systemic treatment group (n=138), and the systemic therapy only group (n=136). The LRT arm demonstrated a notable OS advantage (median OS time, 46 vs. 37 months, P=0.005; 5-year OS rate, 41.6 vs. 24.4%). Unplanned subgroup analyses found that patients with the ER/PR^+ (P=0.008) and $HER2^-$ (P=0.01) subtypes, an age <55 years (P=0.007) and solitary bone-only metastases (P=0.04) benefited the most from LRT (17). Despite more favorable features in the LRT arm, such as a higher proportion of ER/PR^+ (85.5 vs. 71.8%: P<0.05) and lower rates of TNBC (7.3 vs. 17.4%; P<0.05), the MF 07-01 trial highlighted that in a well-selected population of dnMBC, the upfront LRT may lead to a survival benefit (17). In the study by Shien *et al* (55), 344 patients with dnMBC were divided into two groups: The local surgery (n=160) and no local surgery (n=184) groups. A total of 150 (94%) patients in the surgery group had primarily local surgery. Following a median follow-up time of 33 months, the local surgery group attained a superior OS time compared with the no surgery group (median OS time, 27 vs. 22 months; P=0.049), notably in younger individuals (<50 years old) (median OS time, 35 vs. 24 months: P=0.021) (55).

In 2017, Barinoff *et al* (56) re-analyzed two prospective trials conducted in Germany with patients with MBC administered targeted therapy (ML16684: Started in 2000, trastuzumab for $HER2^+$ patients; ML21165: Started in 2007, bevacizumab for $HER2^-$ patients). Among the 570 patients with dnMBC (405 from ML16684 and 165 from ML21165), 2 patients had no data on local resection, 426 patients underwent upfront breast surgery and 142 patients did not undergo breast surgery (56). The surgery cohort had less patients with T4 staging and patients with a lower metastatic tumor burden, but more patients with N3 staging. Other characteristics, such as HR and HER2 status, Eastern Cooperative Oncology Group (ECOG) score and prior palliative management, were equally distributed in the surgery and no surgery cohorts. However, upfront primary surgery failed to bring a benefit for either PFS (surgery vs. no surgery, 13.55 vs. 11.76 months; P=0.18) or OS (surgery vs. no surgery, 34.1 vs. 31.7 months; P=0.23). Nonetheless, in the subgroup without visceral metastasis, the removal of the PT manifested an overt OS time advantage (45.7 vs. 27.2 months; P=0.026) (56).

On the contrary, the ABCSG-28 POSYTIVE trial, a prospective randomized study aiming to evaluate the effect of upfront surgery in untreated patients with dnMBC, drew the opposite conclusion (18). In 2011-2015, 90 untreated candidates with dnMBC were randomly assigned into two groups: The upfront PT surgery followed by systemic therapy (group A, n=45) and systemic therapy only (group B, n=45) groups. Upfront surgery failed to bring any survival benefit (group A vs. B; median survival time, 34.6 vs. 54.8 months, P=0.267; time to distant progression, 13.9 vs. 29.0 months, P=0.0668) (18). This trial was strengthened by a well-balanced design regarding critical prognostic factors, but was criticized for insufficient recruitment and early closing of the study, which underpowered the conclusion (18).

Upfront systemic therapy for dnMBC. Co *et al* (57) and Kwong and Co (58) conducted a retrospective study on 172 patients with dnMBC in Hong Kong between 2007-2016. Following systemic intervention for 8-10 months, resection of the PT was conducted in 91 good responders, who gained a notably improved 5-year OS rate (43.9 vs. 33.9%; P=0.026) (57,58) Additionally, Rao *et al* (59) analyzed the optimal time for surgery for patients with stage IV breast cancer initially with a complete PT excision. In their study, 75 patients were divided into three groups according to the interval between the diagnosis of dnMBC and surgery of the PT: Group 1, 0-2.9 months (n=47); group 2, 3-8.9 months (n=14); and group 3, ≥9.0 months (n=14). Notably, group 2 had the longest MPFS (P=0.0008), despite not having an OS superiority (P=0.12), particularly in patients with a single metastatic site and negative margin (59). A rational explanation for this was that systemic chemotherapy was completed within 3-9 months after diagnosis and those good responders benefited the most from curative surgical management.

However, this conclusion was limited by the small sample size and retrospective nature of the study (59).

Lane *et al* (8) conducted a large-scale retrospective study using the American College of Surgeons National Cancer Database for the years 2003-2012. In total, 24,015 patients with dnMBC who were alive 1 year after diagnosis were enrolled in their study. The candidates were divided into three groups according to the treatment sequence: The systemic treatment only (n=13,505), the upfront surgery before systemic treatment (n=4,552) and the surgery following systemic treatment (n=5,958) groups. The median OS times of these groups were 37.5, 49.4 and 52.8 months, respectively (8). Surgery, whenever it was performed, was closely associated with an improved prognosis, compared with systemic therapy alone (P<0.001). Furthermore, surgery following systemic intervention appeared to prolong the median OS time, compared with the surgery prior to systemic treatment group (8).

For aggressive subtypes of dnMBC, upfront surgery may lead to deleterious consequences. Patients with multiple visceral metastases benefit from first-line systemic treatment other than initial surgery (2). In 2015, the results of the TATA trial, an open-labelled randomized study, were published (19). A total of 350 patients with dnMBC in India responsive to first-line systemic treatment (336 chemotherapy and 14 endocrine) were randomly divided into two groups: The LRT (n=173) and no LRT (n=177) groups. Following a median follow-up time of 23 months, LRT to the PT failed to confer any survival benefit (19). The median OS times and the 2-year OS rates in the LRT and no LRT groups were 19.2 vs. 20.5 months (P=0.79) and 41.9 vs. 43.0%, respectively. The LRT modality also significantly improved the locoregional PFS time (median not attained vs. 18.2 months; P<0.0001), whereas it was detrimental to the distant PFS time (median, 11.3 vs. 19.8 months; P=0.012) (19). That trial was criticized due to insufficient systemic treatment according to the current guidelines. A total of 107 patients (31%) were $HER2^+$, but only 9 patients (8%) underwent anti-HER2 therapy. In addition, only a few patients were administered taxane-based chemotherapy. Moreover, the median OS time in the TATA trial was much shorter than that reported by others such as Lane *et al* (8) and Pons-Tostivint *et al* (16), partly due to the undertreated systemic therapy and later diagnosis of symptoms. Collectively, this underpowered the conclusions made, particularly in the era of a constantly updated systemic strategy.

Pons-Tostivint *et al* (16) published their latest results on 4,276 patients with dnMBC in the NCT03275311 trial in 2018. A total of 1,706 patients underwent LRT, while 2,570 patients did not. The median duration between MBC diagnosis and LRT was 5.7 months. Compared with the TATA trial, all the patients in the NCT03275311 trial received modern systemic therapy (16). In total, 94% of the $HER2^+$ cohort was administered trastuzumab and 90% of the HR^+ candidates were administered endocrine therapy. LRT attained a superior OS time in patients with the $HR^+/HER2^-$ (61.6 vs. 45.9 months; P<0.001) and $HER2^+$ (77.2 vs. 52.6 months; P=0.008) subtypes, but had no effect on OS in the TNBC population. Additionally, in the visceral metastatic subset, LRT also reduced the risk of mortality (16). In a previous retrospective study on 622 patients with dnMBC performed by Cady *et al* (60), primary surgery (n=234) indicated a survival benefit compared with without surgery (n=388; P<0.0001). For the bone metastasis subset (n=255), the survival advantage was overt in the primary surgery group (P<0.0001), but this benefit was reduced after case-matching (n=168; P=0.0003), which reflected the selection bias. Similarly, in the visceral metastatic subgroup (n=159), the survival superiority conferred by primary resection was significant (P=0.0008), but this is not the case after case-matching (n=100; P=0.09) (60). With regards to the order of systemic treatment and primary surgery, it was found that 90% of patients who survived for 2-years were administered chemotherapy initially. However, this survival benefit was not present in the cohort of patients who received surgery immediately after systemic therapy, suggesting that patients with dnMBC who respond robustly to upfront systemic intervention are most likely to benefit from primary surgery (60).

NCT03870919 has been launched to evaluate the OS of combined modality with the CDK4/6 inhibitor, palbociclib, plus letrozole and the most adapted LRT in the treatment of patients with naïve $HR^+/HER2^-$ dnMBC. The ECOG 2108 (NCT01242800) study was designed to clarify the effects of local treatment in patients with stage IV breast cancer. In the 2020 ASCO meeting, the results of the long-awaited ECOG 2108 study were presented in which 390 patients with dnMBC were enrolled, of which 256 patients who responded to initial systemic therapy were randomized to either undergo LCT (surgery and radiation, n=125) followed by systemic therapy or continue with systemic treatment (n=131) (61). However, early LCT failed to bring any survival benefit (neither OS nor PFS). Without LRT, a 2.5-fold higher risk of local failure was posed. Therefore, the ECOG-ACRIN E2108 trial indicated that LRT to the PT should not be recommended to patients with dnMBC for the purpose of survival extension and only reserved for those with well-controlled systemic disease and a progressive PT (61). However, these results were limited for the following reasons: i) Multivariate analysis was not conducted; ii) the inclusion criterion was PT surgery with free margin. However, in the LRT group (n=125), only 109 patients underwent surgery and only 87 (80%) patients had R0 resection; and iii) the T4 and/or N2/3 patients accounted for 48% of the cohort. The effect of the high proportion of patients with a locally advanced status needs to be clarified (61).

Retrospective analyses indicated that for aggressive subtypes, such as multiple visceral metastases or those with heavy tumor burden, upfront LRT was detrimental. Timely and effective systemic treatment to make metastatic lesions controllable and asymptomatic followed by definitive LRT may infer the greatest survival benefit (62,63).

4. Optimal means of LRT

Surgery vs. surgery plus RT. The role of adjuvant RT has been explored by a series of studies. In the study by Altundag (64), 118 patients with dnMBC administered LRT were further divided into three groups: RT only, 2 (1%) patients; surgery only, 54 (29%) patients; surgery followed by RT, 132 (70%) patients. Post-operative RT provided a significant survival advantage (64-66). The 5-year OS and PFS rates in the three groups were 0, 22 and 56% (P<0.001) and 0, 3 and 27% (P=0.001), respectively (66). Additionally, Kim *et al* (67) used the SEER database to address this issue. Following propensity-score

matching, the addition of RT further improved the cancer-specific survival (CSS) of candidates who lived >6 months. The study by Arciero *et al* (25) also favored the addition of RT to surgery of the PT in dnMBC. In the multivariate analysis of the OS of patients with dnMBC who underwent surgery, the administration of RT was an independent factor of an improved outcome (P<0.001) (25).

By contrast, in the analyses performed by Lane *et al* (8), the addition of RT had no association with OS (P=0.83), which was revealed by an adjusted multivariate OS model. However, the majority of patients did not receive RT (59.75%) in this cohort, and the RT administered was not only confined to the PT area (breast, chest or regional lymph nodes; 17.89%), but also included the spine (9.19%) and extremity bones, including the pelvis (4.36%). Therefore, the conclusion of that study could not truly represent the value of RT to the PT region (8).

PT and distant metastatic site resection vs. PT resection vs. distant metastases removal. Tan *et al* (68) conducted a population-based study using the SEER database for the years 2004-2008. A total of 10,441 patients with MBC were divided into four subsets: i) R0 resection (both resection of primary and metastatic sites), 272 (2.61%) patients; ii) PT removal only, 4,025 (38.55%) patients; iii) metastatic lesion resection only, 409 (3.92%) patients; and iv) no surgery, 5,735 (54.93%) patients. The median OS times of the patients in the four groups were 51, 43, 31 and 21 months, respectively (P<0.001) (68). Furthermore, the HR status influenced the survival benefit from surgery. For the HR^+ cohort, the median OS times and 5-year OS rates for R0 resection, primary resection, metastases resection and no resection were 66, 52, 38 and 28 months and 54.1, 44.9, 31.7 and 22.0%, respectively (P<0.001). However, for the HR^- cohort, the median OS times and 5-year OS rates for R0 resection, primary resection, metastases resection and no resection were 18, 24, 12 and 12 months and 26.7, 25.0, 6.8 and 11.8%, respectively (68). In the HR^+ cohort, the R0 resection group attained a further survival benefit compared with the primary resection group (P<0.001), and the same was observed for the metastases resection group compared with the no resection group (68). However, this additional survival advantage disappeared in the HR^- cohort. These findings indicated that HR^+ patients with dnMBC may attain more survival benefits from a more aggressive LRT approach (68).

The addition of post-operative RT to the PT region following surgery may lead to an improved outcome of patients with dnMBC. For HR^+ patients with dnMBC, distant metastatic site resection could also lead to an improved survival outcome.

5. Population most likely to benefit from LRT

Bone-only metastases. In 2006, Rapiti *et al* (10) conducted a study including 300 patients with dnMBC recorded at the Geneva Cancer Registry between 1977-1996. After adjusting for other cancer prognostic confounding factors, complete resection of the PT reduced the risk of breast cancer-specific mortality by 40% (P=0.049) (10). This benefit was particularly evident for patients with dnMBC and bone metastasis only. The metastatic pattern was a vital covariable that determined the prognosis of dnMBC (10). Wang *et al* (69) retrospectively analyzed 8,142 patients with dnMBC from 2010-2015 using the SEER database. By comparing the surgical (n=1,891) and non-surgical groups (n=6,251), they noted that surgery provided a survival advantage in those with a bone-only metastasis or with multiple metastases including the bone (P<0.05), but a survival inferiority in those with multiple metastases only in visceral organs (P<0.05) (69). The aforementioned MF 07-01 study, revealed that the solitary bone-only metastatic subset benefited from LRT (17). However, the other three well-known randomized trials, TATA (19), TBCRC 013 (47) and POSYTIVE (18), failed to identify the superiority brought by surgery. Notably, the proportion of bone-only metastasis in the TATA (19), TBCRC 013 (47), POSYTIVE (18) and MF 07-01 (17) studies was 28, 37, 38 and 46%, respectively. The highest ratio of patients with bone-only metastasis was found in the MF 07-01 study, which largely determined the positive results of the study (17).

Oligometastatic disease or low metastatic burden. Barinoff *et al* (56) found that the number of involved sites was closely associated with PFS and OS in the dnMBC cohort. Multivariate analysis determined that <3 metastatic sites led to an improved PFS and OS in patients with dnMBC (P=0.0005 and P=0.00051, respectively). Xiong *et al* (3) retrospectively reviewed 313 patients with dnMBC from January, 2006 to April, 2013 at the Sun Yet-sen University Cancer Center. Patients who underwent local surgery (n=188) had a notable median OS time advantage compared with those who did not undergo surgery (n=125) (78 vs. 37 months; P=0.002). Stratified survival analysis revealed that bone metastasis plus a PT <5 cm, ≤3 metastatic sites, or soft tissue metastasis predicted a benefit from local removal (3). Bafford *et al* (9) analyzed the impact of staging for breast surgical removal in patients with dnMBC. The 147 patients enrolled were divided into two groups: The surgery (n=61) and non-surgery (n=86) groups. After adjusting for age, number of metastatic sites, ER/Her2neu status and the use of chemotherapy, trastuzumab and endocrine therapy, the surgery group gained a significantly improved OS time compared with the non-surgery cohort (4.13 vs. 2.36 years; P=0.003). However, the number of metastases in the non-surgery group was markedly higher than in the surgery group (≥3, 84 vs. 41%) (9). Notably, in the surgery group, 36 patients underwent surgery before the diagnosis of metastatic disease. The 25 patients diagnosed with stage IV pre-operatively had a very similar OS time to those without surgery (2.4 vs. 2.36 years), while the patients undergoing surgery before metastatic diagnosis had a notably improved OS time (4.05 years) (9). This may be explained by the fact that those who underwent resection of the intact PT before a stage IV diagnosis were typically asymptomatic and with a limited metastatic burden, which contributed to a relatively optimal outcome (9). Previously, Lin *et al* (49) identified 8,582 patients with dnMBC from 2010-2014 using the SEER database, and further subdivided M1 into three groups. Patients with an M1a status (meaning a single metastatic site, except the liver and brain) gained the most benefit from PT surgery.

HR^+. In a retrospective study conducted by Tan *et al* (68), resection of both the primary and metastatic lesions for stage IV BC led to the optimal survival of patients with HR^+ breast cancer.

In a single institutional analysis of 111 patients with dnMBC conducted by Samiee *et al* (70), HR^+ and surgical removal both indicated a better prognosis (P<0.001 and P=0.041, respectively), using multivariate analysis. The ESME-MBC study demonstrated a median OS time of 42.12 months for newly diagnosed $HR^+/HER2^-$ patients with dnMBC (38). In another study, HR positivity predicted a favorable outcome in the surgical group independently, following multivariate analyses. ER positivity was found to be the only good prognostic predictor in surgical patients with dnMBC (57).

Favorable profile and relatively long survival. Rashaan *et al* (71) demonstrated that a younger age (P=0.03) and an absence of complications (P=0.03) were independent prognostic factors for improved survival in the dnMBC cohort receiving surgery. In the retrospective study by Shien *et al* (55), PT surgery conferred an OS advantage in young candidates (P=0.021), but not in older candidates (>51 years old, P=0.665). Blanchard *et al* (46) also demonstrated that the subpopulation of relatively long survivors of dnMBC gained more benefit from definitive surgery. For those patients who underwent surgery and survived for >2 years (n=119), survival was significantly improved compared with no primary surgery (n=51; P=0.0037) (46).

Prediction scoring model. Yoo *et al* (7) developed and validated a survival prediction-scoring model using the Korean Breast Cancer Registry database, aiming to identify the subset of long-term survivors of dnMBC who underwent surgery of the PT. Their study excluded those who received resection of metastatic foci. The 2,232 enrolled patients were divided into three groups, according to the surgery type: Surgery (n=1,541), non-surgery (n=588) and partial surgery (n=103; only breast or axillary removal) groups. The surgery cohort had a significantly improved median survival time compared with the non-surgery group (53 vs. 31 months; P<0.001) (7). There was no significant difference with respect to the median OS time between the non-surgery and partial surgery cohorts (37 vs. 31 months; P=0.113). The OS prediction-scoring model for patients with dnMBC undergoing surgery of the PT was established based on the following seven factors: T stage, tumor grade, lymphovascular invasion (LVI), ER expression, and the levels of Ki-67, CA 153 and alkaline phosphatase (7). The patients in the surgery group were further grouped into four subsets: Subsets with a score of 0-3, 4-5, 6-7 or 8-10, with clearly defined 3-year survival rate outcomes (87.3%, score 0-3; 68.4%, score 4-5; 48.2%, score 6-7; 35.3%, score 8-10). The group with a score 0-3 had a significant advantage as regards OS, demonstrated both in the discovery cohort (87.3%; P<0.001) and in the validated cohort (85.9%; P<0.001). This tool provided a method to identify the candidates with dnMBC who would benefit the most from primary surgery (7).

Since dnMBC is highly heterogeneous, multiple factors, including the status of the patient, tumor pathology, biology and metastatic pattern, may help to determine the cohorts most likely to benefit from LRT. A younger age and a good general condition without complications, a smaller tumor, a lower tumor grade, no LVI, HR positivity, bone-only metastasis and low metastatic burden have been found to be associated with an improved outcome. In the future, a gene signature of dnMBC may help to identify the patients who will benefit the most from LRT. Additionally, an improvement in systemic intervention and new drugs may achieve the complete remission of metastatic lesions, which will result in more candidates who will benefit from definitive LRT. In clinical practice, the flow diagram with therapeutic options presented in Fig. 1 may aid in decision-making when treating patients with dnMBC.

6. Mechanisms through which LRT benefits patients with dnMBC

The crosstalk between the primary tumor and metastatic foci. Previously, some studies proposed that resection of the PT would promote the progression of distant metastasis, partly mediated by the angiogenesis rebounds and the growth factor surge responding to the surgical wounding (72,73). It was suggested that the PT secreted angiogenesis inhibitors, such as angiostatin, controlling the growth of metastatic lesions (74). PT removal would therefore alter the growth kinetics of the residual tumor (75). However, these theories resulted from an animal model with an unclear clinical translational implication (76).

The metastasis of a tumor is comprehensive, involving multiple factors and associations. Under certain incentives, such as hypoxia, tumor cells develop epithelial-interstitial transformation and increase their invasive ability (77). Accordingly, the interactions with stromal cells in the surrounding microenvironment degrade, restructuring the extracellular matrix and allowing tumor cells to invade the basement membrane and enter blood vessels. In this process, there are approximately three mechanisms involved. Firstly, the PT will secrete relevant cytokines, such as TGF-β, VEGF, matrix metalloproteinases and the remodeling enzyme, lysyl oxidase, and promote the migration of tumor cells. Secondly, endocrine signaling from the primary foci recruits mesenchymal stem cells (MSCs) from the bone marrow into the microenvironment of the primary foci to promote metastasis (78-80). Thirdly, pro-inflammatory and pro-angiogenic factors secreted by the primary foci, such as TNF-α, IL-8 and VEGF (78,81-83), which increase angiogenesis and vascular permeability of the primary foci, facilitate the invasion of blood vessels by tumor cells. Circulating tumor cells (CTCs) form clusters and migrate in the bloodstream (84-86). Various cytokines, chemokines and growth factors secreted by the primary foci and MSCs recruited from the bone marrow also enter the target organ in advance, which shapes the targeted microenvironment and forms a pre-metastatic niche to welcome the arrival of the CTCs (83,87-92). Organ specificity during metastasis is regulated by chemokines, exosomes, integrins and other factors, such as chemokine receptors (87-89,93-97). If CXCR4 is highly expressed by the PT, the bone, lungs and brain are prone to metastasis due to the extensive expression of CXCR4 ligand-CXCL12. The new metastasis may originate from the PT or from an existing metastasis (98-100). Crosstalk exists between the primary and secondary tumor. The PT secretes highly effective immunosuppressive molecules, such as TGF-β, VEGF, IL-10, inflammatory factors (such as IL-6 and IL-8) and angiogenesis inhibitors (such as angiostatin and endostatin), to regulate growth of the secondary tumor (Fig. 2) (78,81-83).

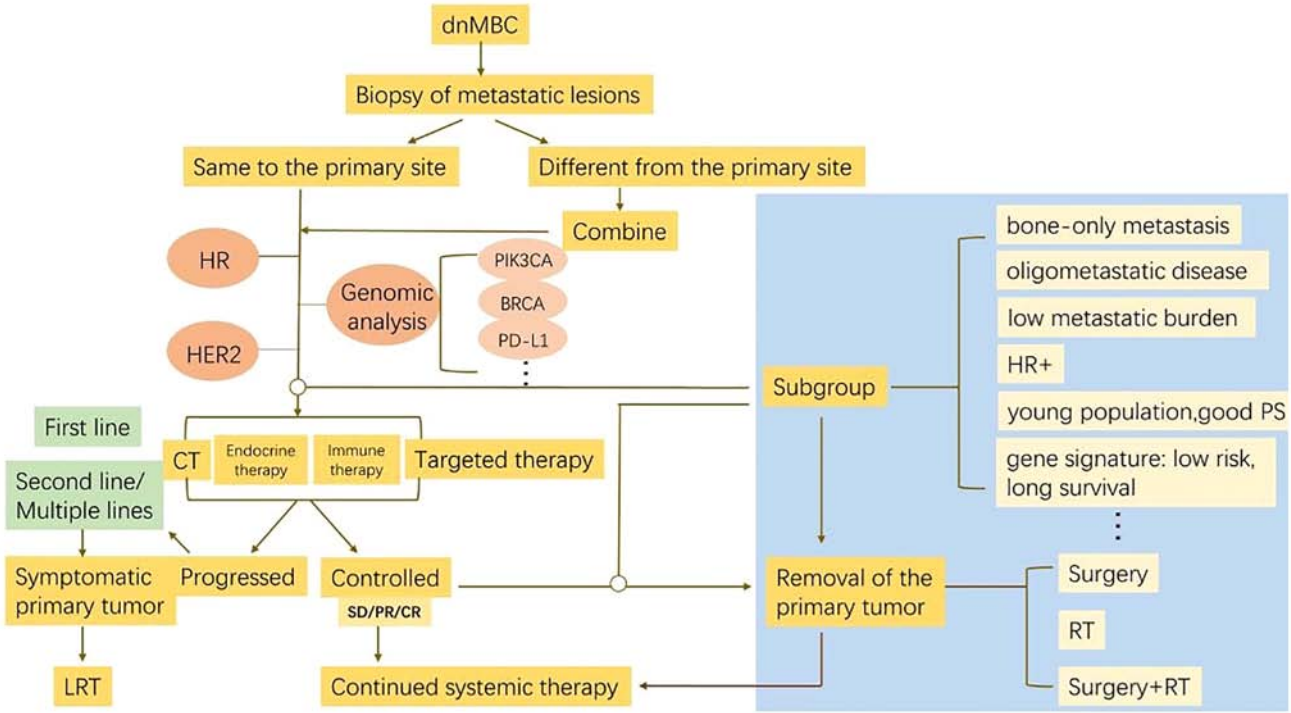

Figure 1. Flow diagram with therapeutic options for patients with dnMBC. When treating patients with dnMBC, the molecular typing, including HR, HER2 and Ki-67 expression, and genomic analysis of both the primary and metastatic tumors are fundamental. Upfront systemic strategies are tailored according to the tumor biology and status of the patient. For good respondents to upfront systemic therapy and subgroup of favorable profiles, radical LRT including PT surgery followed by RT and resection of distant metastases will be recommended. LRT should also be administered if PT is still symptomatic. Therefore, the treatment paradigm for dnMBC may change from 'palliative LRT' into 'curative LRT' in highly selected entity with careful evaluation. dnMBC, *de novo* metastatic breast cancer; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; LRT, local radiotherapy; PT, primary tumor; PD-L1, programmed cell death ligand 1; RT, radiotherapy.

Control of the PT decreases tumor burden and eliminates the source of dissemination. Total tumor burden has been revealed to be closely linked with survival (44,101). The level of CTCs is also an independent prognostic factor for the PFS and OS of patients with MBC (102,103). Similarly, the PT of dnMBC serves as another metastatic site or source of dissemination (10,13,44). Resection of the PT can block the continued production of CTCs, reduce subsequent metastasis and improve prognosis (46-49). In the study conducted by Rapiti *et al* (10), surgery of the PT with a positive margin failed to improve survival of patients with dnMBC compared with patients who did not undergo surgery. The 5-year CSS rates of patients who underwent primary surgery with negative margins, positive margins, an unknown margin status or who did not undergo surgery were 27, 16, 12 and 12%, respectively (P=0.0002) (10). Yoo *et al* (7) conducted a retrospective study on dnMBC with a larger sample size. Patients were further categorized into three groups according to the following: The surgery (n=1,541), partial surgery (n=103, no definite resection of the PT) and non-surgery (n=588) groups. The definite surgery cohort demonstrated a significant OS time advantage compared with the non-surgery group (53 vs. 31 months; P<0.001), which was not observed in the partial surgery group (37 vs. 31 months; P=0.113) (7). Additionally, Hazard *et al* (104) verified that the chest wall status had a direct effect on the OS of patients with dnMBC. Compared with a symptomatic chest wall, the presence of a free or asymptomatic status could notably decrease the hazard ratio of mortality (hazard ratio, 0.415). Multivariate analysis further supported that primary surgery markedly reduced the probability of uncontrolled chest wall status (104). Furthermore, MSCs recruited by the PT from the bone marrow release paracrine signals, such as C-C motif ligand 5, which interact with C-C motif receptor 5 on cancer cells, induce the metastasis of primary cancer cells and maintain the metastatic phenotype of cancer cells (79). Cancer stem cells (CSCs) in the PT, are able to self-renew, differentiate and activate, and are the main source of continuous dissemination and metastasis (52). These findings highlight that the complete clearance of the PT, eradicating the source of metastasis, may translate into a survival benefit (101).

Enhancing the sensitivity to therapy. Maximal tumor debulking markedly increases drug accessibility (101). Notably, necrotic, hypoxic and avascular tumors exhibit resistance to chemotherapy or RT. Hazard *et al* (104) demonstrated that surgery improved the local control (S vs. NS: 36/44 82% vs. 20/59 34%, P=0.001) and prolonged time to first progression (P=0.015) in dnMBC. In total, 18.2% (8/44) patients in the surgery group also experienced cancer relapse following LRT (104). The removal of these tumors could limit the emergence of treatment-resistant cells, resulting in an increased sensitivity to treatment (12,105). Additionally, CSCs are resistant to common anticancer strategies. Eradiation of the PT will therefore improve treatment efficacy (54-60,62).

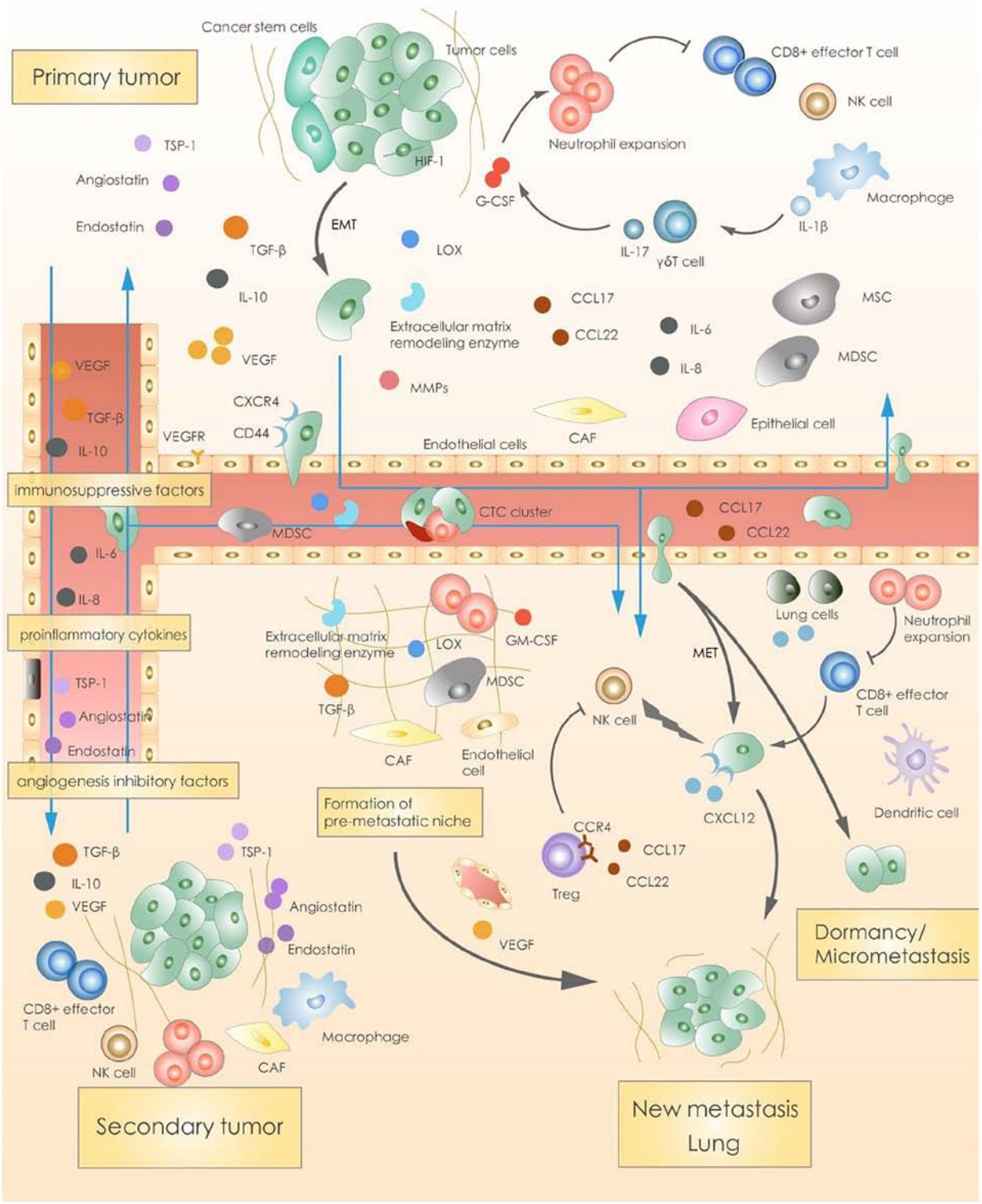

Figure 2. Crosstalk between the primary and secondary/metastatic tumor. The primary tumor secretes relevant cytokines and promote the migration of tumor cells. Endocrine signaling from the primary foci recruits MSCs from the bone marrow into the microenvironment of the primary foci to promote metastasis. Pro-inflammatory and pro-angiogenic factors secreted by the primary foci, which increase angiogenesis and vascular permeability of the primary foci, facilitate invasion of blood vessels by tumor cells. Circulating tumor cells form clusters and migrate into the bloodstream. Organ specificity during metastasis is regulated by this crosstalk between the primary and secondary/metastatic tumor. MSCs, mesenchymal stem cells; TSP-1, thrombospondin 1; EMT, epithelial-mesenchymal transition; HIF-1, hypoxia-inducible factor-1; MMPs, matrix metalloproteinases; G-CSF, granulocyte colony-stimulating factor; CAF, cancer-associated fibroblast; GM-CSF, granulocyte macrophage colony-stimulating factor; MET, mesenchymal-epithelial transition.

Positive immunomodulation. The tumor evolution of some dnMBC patients is related to immune factors and benefit most from removal of the PT (2). In a 4T1-bearing mammary carcinoma mouse model, both antigen specific T-cell proliferation and antibody responses were markedly suppressed compared with tumor-free mice. In patients with BC, the levels

Table I. Published studies on LRT for dnMBC.

Positive results							
Author(s)/trial	Year of publication/ PMID	Country	Study nature	Design	Outcome	Limitation	(Refs.)
Khan *et al*	2002/PMID: 12407345	USA	Retrospective	Non-surgery (n=6,861); surgery (n=9,162); partial mastectomy (PM)(n=3,513); total mastectomy ™ (n=5,649)	Mean survival: Non-surgery, 19.3 months; PM, 26.9 months; TM, 31.9 months. 3-Year survival: Non-surgery, 17.3%; PM, 27.7%; TM, 31.8%	Patients with 1 metastatic site more likely to undergo mastectomy	(44)
Rapiti *et al*	2006/PMID: 16702580	Switzerland	Retrospective	Surgery (n=127); mastectomy (n=87); tumorectomy (n=40); margin-(n=61); margin + (n=33); margin unknown (n=33); non-surgery (n=173)	Primary tumor complete resection (margin -) reduced 40% breast cancer specific mortality risk compared with those without surgery (P=0.049) and this benefit wasparti-cularly obvious in the subgroup of bone metas-tasis only (P=0.001)	Retrospective nature despite of adjusting for other main factors of prognosis and avoiding selection bias using subgroup analyses	(10)
Babiera *et al*	2006/PMID: 16614878	USA	Retrospective	Non-surgery (n=142); surgery (n=82); segmental mastectomy (n=39); mastectomy (n=43)	After adjusting, surgery group: A trend for improved OS (P=0.12); improved metastatic PFS (P=0.0007)	Baseline unbalance: Surgery group; younger, lower tumor burden, more $HER2^+$, more liver metastases, more chemotherapy as initial systemic therapy	(11)
Fields *et al*	2007/PMID: 17687611	USA	Retrospective	Surgery (n=187); non-surgery (n=222)	After adjusting: Median OS: S vs. NS (31.9 vs. 15.4 months, P<0.0001)	Baseline unbalance: Surgery group; younger, smaller\ primary tumor and lower proportion of bone metastasis	(13)

Table I. Continued.

Positive results

Author(s)/trial	Year of publication/ PMID	Country	Study nature	Design	Outcome	Limitation	(Refs.)
Gnerlich *et al*	2007/PMID: 17522944	USA	Retrospective	Surgery (n=4,578); non-surgery (n=5,156)	Median OS: S vs. NS (36 vs. 21 months, P<0.001, alive; 18 vs. 7 months, P<0.001, did not survive).	Surgery: Younger, diagnosed earlier, more likely to be Caucasian, married, <5 cm, grade III, HR^+	(12)
Blanchard *et al*	2008/PMID: 18438108	USA	Retrospective	Surgery (n=242); non-surgery (n=153)	Median OS: S vs. NS (27.1 vs. 16.8 months, P<0.0001).	Selection biases; margin status unclear in most cases	(46)
Cady *et al*	2008/PMID: 18726129	USA	Retrospective	Surgery (n=234); non-surgery (n=388)	OS: S vs. NS (P<0.0001).	Selection bias	(60)
Hazard *et al*	2008/PMID: 18780312	USA	Retrospective	Surgery (n=47): 26 diagnosed IV post-operatively; 24 systemic therapy first; non-surgery (n=64)	Local control: S vs. NS: 36/44 82% vs. 20/59 34%, P=0.001; time to first progression (TTFP): S: prolonged, P=0.015	S: Younger (P=0.033); more HR^- (P=0.0005); more RT (P<0.001); included those with metastasis within 6 months of diagnosis	(104)
Ruiterkamp *et al*	2009/PMID: 19398188	The Netherlands	Retrospective	Surgery (n=288); non-surgery (n=440)	S vs. NS: (median OS: 31 vs. 14 months, 5-year OS rate: 24.5% vs. 13.1%, P<0.0001).	S: Younger, smaller T, less likely to have visceral metastases or co-morbidity, more often with RT/systemic therapy	(107)
Bafford *et al*	2009/PMID: 18581232	USA	Retrospective	Surgery (n=61); n=36, surgery before the diagnosis of metastatic disease; n=25, diagnosed with IV stage pre-operatively; non-surgery (n=86)	After adjusting: OS: S vs. NS (4.13 vs. 2.36 years, P=0.003)	36 Patients underwent surgery before the diagnosis of metastatic disease; stage migration	(9)
Shien *et al*	2009/PMID: 19212646	Japan	Retrospective	Surgery (n=160); 94%: Local surgery as primary therapy, no post-operative RT; non-surgery (n=184)	OS of patients with primary tumor resection improved (P=0.049); younger patients (<50 years,	Surgery group: Younger, earlier in the study period, more bone/soft metastasis, more hormonal	(55)

Table I. Continued.

Positive results							
Author(s)/trial	Year of publication/ PMID	Country	Study nature	Design	Outcome	Limitation	(Refs.)
					P=0.023), and with soft tissue or bone metastases (P=0.013)	therapy	
Leung *et al*	2010/PMID: 19375721	USA	Retrospective	Surgery (n=52, 33%); non-surgery(n=105, 67%)	Median OS: Surgery, 25 months; non-surgery, 13 months; Wilcoxon test (P=0.004) and log-rank test (P=0.06)	Retrospective study: Unrecognized biases	(108)
Pathy *et al*	2011/PMID: 21858791	Malaysia	Retrospective	Surgery (n=139), non-surgery (n=236)	Surgery vs. non-surgery group:2-year OS% (46.3 vs. 21.2%)	Selection biases	(109)
Rashaan *et al*	2012/PMID: 22032912	The Netherlands	Retrospective	Surgery (n=59), non-surgery (n=112)	Younger patients (P=0.03) and individuals without comorbidities (P=0.03) that underwent surgery had an improved survival	Surgery group had a younger age, clinical T stage and no medication use	(71)
Samiee *et al*	2012/PMID: 22876156	Canada	Retrospective	Surgery (n=48, 29 had surgery before metastatic diagnosis); non-surgical group (n=63)	Surgery vs. non-surgery group: OS (49 vs. 33 months,P=0.01);symptomatic local progression (14 vs. 44%, P<0.001).	Surgical group: Less likely to present with T4 (23 vs. 35%), N3 (8 vs. 19%) and visceral metastasis (67 vs. 73%)	(70)
Bertaut *et al*	2015/PMID: 25757548	France	Retrospective	Total: 232; surgery (n=92); non-surgery (n=139); missing data (n=1)	Surgery of PT: Improved survival (relative excess rate = 0.43; 95% CI: 0.28-0.68)	18 (40%) $HER2^+$ patients did not receive trastuzumab	(110)
Tan *et al*	2016/PMID: 27542240	USA	Retrospective	272 (2.61%) R0 resection (both primary and metastatic sites resection); n=4,025 (38.55%), primary tumor removal only; n=409 (3.92%),	The median OS of the four groups was 51, 43, 31 and 21 months (P<0.001). HR^+: The median OS and 5-year OS	Several important factors including performance status, number of metastatic sites, HER2 status,	(68)

Table I. Continued.

Positive results							
Author(s)/trial	Year of publication/ PMID	Country	Study nature	Design	Outcome	Limitation	(Refs.)
				metastatic lesion resection only; n=5,735 (54.93%), no surgery	rates for R0 resection,primary resection, metastases resection and no resection were 66, 52, 38, 28 months, and 54.1, 44.9, 31.7 and 22.0%, respectively (P<0.001). HR-: The median OS and 5-year OS rates for R0 resection, primary resection, metastases resection and no resection were 18, 24, 12, 12 months, and 26.7, 25.0, 6.8 and 11.8%, respectively. The R0 resection and the primary tumor resection both markedly prolonged the OS compared with the no resection group, but the metastatic group did not have this benefit. R0 resection failed to attain survival advantage compared with the group of primary tumor resection only (P=0.691)	endocrine therapy, chemotherapy and the size of the metastases were not accessible	
Thomas *et al*	2016/PMID: 26629881	USA	Retrospective	Surgery (n=8,330), non-surgery (n=13,042)	Surgery vs. non-surgery group: Median OS (28 vs. 19 months)	Excluded a large group of patients who received radiation as the initial course of therapy	(2)

Table I. Continued.

Positive results							
Author(s)/trial	Year of publication/ PMID	Country	Study nature	Design	Outcome	Limitation	(Refs.)
Barinoff *et al*	2017/PMID: 28735068	Germany	Retrospective	Upfront breast surgery (n=426); no surgery (n=142)	Surgery vs. no surgery: PFS (13.6 vs. 11.8 months, P=0.18) or OS (34.1 vs. 31.7 months, P=0.23); OS (45.7 vs. 27.2 months, P=0.026); subgroup without visceral metastasis	Unbalanced baseline characteristics: Surgery (less T4 and lower metastatic tumor burden but more N3)	(56)
Yoo *et al*	2017/PMID: 28573447	Korea	Retrospective	Surgery (n=1,541), non-surgery (n=588) partial surgery group (n=103, only breast or axillary removal)	Surgery vs. non-surgery group: OS (53 vs. 31 months, P<0.001); non-surgery vs. partial surgery cohorts (37 vs. 31 months, P=0.113)	Data on the metastatic sites were unavailable; unbalanced baseline characteristics: Surgery (smaller tumor, less axillary nodal involvement, lower grade and Ki-67, ductal carcinoma and clinical factors suggesting a lower tumor burden)	(7)
Soran *et al*	2018/PMID: 29777404	Turkey	Prospective randomized multicenter, phase III	LRT followed by ST (n=138) ST alone (n=136)	LRT vs. no LRT; hazard of mortality, 34% lower; median OS, 46 vs. 37 months (P=0.005); 5-year survival rate, 41.6 vs. 24.4%; suitable candidates: (ER)/(PR)(+) (P=0.01), (HER2)(-) (P=0.01), <55 years (P=0.007), solitary bone-only metastases (P=0.04)	Unbalanced baseline characteristics: LRT, higher rates of ER/PR^{+}(85.5% vs. 71.8%; P=0.01) and lower rates of triple-negative tumors (7.3 vs. 17.4%; P=0.01)	(17)

Table I. Continued.

Positive results

Author(s)/trial	Year of publication/ PMID	Country	Study nature	Design	Outcome	Limitation	(Refs.)
Xiong *et al* (3)	2018/PMID: 30200932	China	Retrospective	Surgery (n=188), non-surgery (n=125)	Surgery vs. non-surgery group: Median OS (78 vs. 37 months, P=0.002)	Single center; selection bias	
Pons-Tostivint *et al*	2019/PMID: 30539492	France	Retrospective	LRT (n=1,706); surgery (26%); RT (31%); S + R, 43%; no LRT (n=2,570)	LRT, improved OS; subgroup analysis: LRT with improved median OS in $HR^+/HER2^-$ (61.6 vs. 45.9 months, P<0.001), $HER2^+$ (77.2 vs. 52.6 months, P=0.008), but not in TNBC, and mortality risk reduction in visceral metastatic patients (P<0.001)	Details of surgical margin and RT, PS were unavailable The duration of systemic therapy was longer in LRT (16.4 vs.7.8 months)	(16)
Lane *et al*	2019/PMID: 29227346	USA	Retrospective	Systemic treatment alone (n=13,505), upfront surgery prior to systemic treatment (n=4,552) and surgery after systemic treatment (n=5,958)	The median OS of the three groups was 37.5, 49.4 and 52.8 months, respectively. Surgery, whenever it was performed, was closely associated with an improved prognosis compared with systemic therapy alone (P<0.001)	Following multivariable adjustment, the group which underwent systemic therapy prior to surgery was more likely to undergo mastectomy	(8)
Arciero *et al*	2019/PMID: 31087448	USA	Retrospective	Surgical group (n=5,202) and non-surgical group (n=6,492)	Propensity score matching revealed an obvious survival benefit in the surgical cohort, regardless of the administration of systemic intervention (P<0.001)	Surgical arm: Smaller tumor (T1) and higher burden of nodes (N2-3)	(25)

Table I. Continued.

Author(s)/trial	Year of publication/ PMID	Country	Study nature	Design	Outcome	Limitation	(Refs.)
Positive results							
Co *et al*	2019/PMID: 30825858	Hong Kong, SAR	Retrospective	LRT (n=91) No LRT (n=81)	LRT vs. no LRT; median OS, 55 vs. 40 months; 2-year OS, 84.5 vs. 73.7%; 5-year OS, 43.9 vs. 33.9% (P=0.026)	Surgical group: Significantly younger	(57)
Lopez-Tarruella *et al*	2019/PMID: 31882586	Spain	Retrospective	Surgery, 44.5%; no surgery, 55.5%	Surgery vs. no surgery: OS, 39.6 vs. 22.4 months (P<0.0001)	Surgery group: Younger, smaller tumors, more bone and oligometastatic disease, less visceral metastasis	(111)
Pons-Tostivint *et al*	2020/PMID: 31931289	France	Retrospective	n=1,965; n=891 LRT including 41.1% (n=366) exclusive radiotherapy, 13.7% (n=122) exclusive surgery, 45.2% (n=403) bimodality therapy (surgery + radiotherapy)	Following propensity score matching, exclusive radiotherapy, surgery and bimodality therapy: Significantly improved progression-free survival in multivariable analysis	Selection biases	(112)
Negative results							
Fitzal *et al* ABCSG-28 POSYTIVE	2019/PMID: 29697452	Austria	Prospective, randomized, phase III	Upfront surgery of the primary tumor then systemic therapy (Arm A n=45) or primary systemic therapy (Arm B, n=45)	A vs. B: Median OS, 34.6 vs. 54.8 months (P=0.267); time to distant progression, 13.9 vs. 29.0 months (P=0.0668)	Poor recruitment, early closing	(18)
Badwe *et al* TATA NCT00193778	2015/PMID: 26363985	India	Prospective randomized	First-line systemic therapy: LRT (n=173); no LRT (n=177)	LRT vs. no LRT: Median OS, 19.2 vs. 20.5 months (P=0.79); 2-year OS: 41.9 vs. 43.0%; median loco-regional progression-free survival, not attained vs.	Later diagnosis, systemically undertreated	(19)

Table I. Continued.

Negative results							
Author(s)/trial	Year of publication/ PMID	Country	Study nature	Design	Outcome	Limitation	(Refs.)
					18.2 months, P<0.0001; distant progression-free survival: 11.3 vs. 19.8 months, P=0.012		
Rosche *et al*	2011/PMID: 22104157	Germany	Retrospective	Surgery (n=35), non-surgery (n=26), surgery of the primary tumor performed 0-19 months after dnMBC diagnosis; 20/35 in surgery, 7/26 in non-surgery received RT	Surgery vs. no surgery: OS and progression-free survival, no difference	Surgery group: Good profile including younger age, only one metastatic lesion (P=0.01) and performed RT more frequently (P=0.04)	(113)

dnMBC, *de novo* metastatic breast cancer; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; LRT, local radiotherapy; RT, radiotherapy; ST, systemic therapy; OS, overall survival.

Table II. Important clinical trials of LRT for dnMBC.

Trial ID	Name	Country	Intervention model	Start sate	Estimated primary completion date	Estimated studycomp-letion date	Arm	Primary outcome measure	(Refs.)
NCT03870919	Locoregional Treatment and Palbociclib in *de Novo*, Treatment Naive, Stage IV ER+, HER2- Breast Cancer Patients (PALATINE)	France	Single group assignment	October 23, 2019	October 23, 2023	October 23, 2027	Palbociclib + LRT: Palbociclib + letrozole for 24-26 weeks, then the most adapted LRT (surgery with or without RT, or RT). Palbociclib continued until progression	OS	
ECOG 2108 NCT01242800	Early Surgery or Standard Palliative Therapy in Treating Patients With Stage IV Breast Cancer	Eastern Cooperative Oncology Group	Randomized	February 8, 2011	June 30, 2022	December 21, 2022	Arm I: Standard palliative therapy (RT/surgery/both), to address symptoms; Arm II: Breast-conserving therapy (BCT) or total mastectomy (R0 surgery) + adjuvant RT	OS	(61)
NCT00941759	Analysis of Surgery in Patients Presenting With Stage IV Breast Cancer	USA	Observational	July, 2009	July, 2021	July, 2024	Known or suspected Stage IV disease and an intact primary: Research core needle biopsy of the primary tumor/original diagnostic biopsy material/diagnostic biopsy of a metastatic site/ blood draw; unsuspected metastatic disease W/I 3 months of primary b: blood sample/	Response to first-line therapy, frequency and proportion of surgical referral	

Table II. Continued.

Trial ID	Name	Country	Intervention model	Start sate	Estimated primary completion date	Estimated studycomp-letion date	Arm	Primary outcome measure	(Refs.)
							paraffin tissue from the prior surgical procedure and diagnostic biopsy of a metastatic site/fresh frozen tissue		
NCT00193778	Assessing Impact of Loco-regional Treatment on Survival in Metastatic Breast Cancer at Presentation	India	Randomized	February, 2005	March, 2020	March, 2020	Arm I: Standard loco-regional treatment i.e., surgery (modified radical mastectomy (MRM)/ simple SMAC/ BCT) +/- RT; Arm II: Not receive any loco-regional treatment	OS	(19)
NCT02089100	Trial of Superiority of Stereotactic Body Radiation Therapy in Patients With Breast Cancer (STEREO-SEIN)	France	Randomized	February, 2014	February, 2020	February, 2023	ARM1: SBRT to all metastases + systemic therapy ARM2: No specific treatment to the oligometastatic site other than palliation	PFS	
NCT02364557	Testing Whether Treating Breast Cancer Metastases With Surgery or High-Dose Radiation Improves Survival	USA	Randomized	December 24, 2014	December 31, 2022	December 20, 2026	Arm 1 (standard of care): Systemic therapy; Arm2: Stereotactic radiosurgery, surgery + systemic therapy	PFS, OS	

dnMBC, *de novo metast*atic breast cancer; LRT, local radiotherapy; RT, radiotherapy; ST, systemic therapy; OS, overall survival; PFS, progression-free survival.

of cytokines produced by $CD4^+$ and $CD8^+$ T cells, including IL-2, IFN-γ, TNF-α and IL-4, were markedly decreased compared with the healthy population (63,64). Tumor cells can synthesize and secrete various immunosuppressive factors, such as TGF-β and VEGF, which inhibit effector cells (65). Myeloid-derived suppressor cells play a vital role in immune suppression in patients with BC (66,67). Removal of the PT helps to restore both antibody and cell-mediated immune responses, which manifests as an activated macrophage and dendritic cell function, even in the presence of metastatic disease (100). Moreover, the PT harbors a certain humoral resistance that does not belong to or at least develops slowly in the metastatic lesions. The eradication of this dependent relationship existing between the primary and metastatic foci by PT removal causes the disseminated lesions to be more vulnerable to therapy (106).

7. Conclusions and future perspectives

dnMBC has long been considered incurable, which has been challenged with the new understanding of tumor biology and the advent of novel systemic strategies. The heterogeneity of dnMBC leads to difficulties in assessing the suitability of candidates, and the optimal time and means for LRT. The results from published (Table I) and ongoing trials (Table II) have demonstrated that initial effective systemic management to control the metastatic lesions followed by definitive LRT are most likely to improve the OS of patients with dnMBC. The updated results of the long-awaited ECOG-ACRIN E2108 trial revealed that early LRT did not attain any survival advantage (OS or PFS) for patients with dnMBC, but did markedly decrease the local failure risk (61). Thus, patients with dnMBC with a satisfactory control of distant metastases and a progressive local tumor may benefit from LRT. In clinical practice, when treating patients with dnMBC, the molecular typing, including HR, HER2 and Ki-67 expression, and genomic analysis of both the primary and metastatic tumors are fundamental. Upfront systemic strategies, including chemotherapy, endocrine therapy, immunotherapy and targeted therapy are tailored according to the tumor biology and status of the patient. For good respondents (stable disease/partial remission/complete remission) and subgroups with favorable profiles, such as bone-only metastasis, oligometastatic disease or a low metastatic burden, HR^+, young patients without any complications, and a gene signature with a low risk and long survival, will be recommended radical LRT, including PT surgery followed by RT and the resection of distant metastases. For patients with progressive disease, second line or multiple systemic strategies can be administered. LRT should be administered if the PT is still symptomatic. Therefore, the treatment paradigm for dnMBC may change from 'palliative LRT' to 'curative LRT' in the most suitable population, which translates into a survival advantage.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Natural Science Foundation of China (grant no. 82073475).

Availability of data and materials

Not applicable.

Authors' contributions

BL was a major contributor to the writing of the manuscript and HL revised it critically. ML revised the manuscript, reviewed the literature and gave the final approval of the version to be submitted. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Siegel R, Naishadham D and Jemal A: Cancer statistics, 2013. CA Cancer J Clin 63: 11-30, 2013.
2. Thomas A, Khan SA, Chrischilles EA and Schroeder MC: Initial surgery and survival in stage IV breast cancer in the United States, 1988-2011. JAMA Surg 151: 424-431, 2016.
3. Xiong Z, Deng G, Wang J, Li X, Xie X, Shuang Z and Wang X: Could local surgery improve survival in de novo stage IV breast cancer? BMC Cancer 18: 885, 2018.
4. Eng LG, Dawood S, Sopik V, Haaland B, Tan PS, Bhoo-Pathy N, Warner E, Iqbal J, Narod SA and Dent R: Ten-year survival in women with primary stage IV breast cancer. Breast Cancer Res Treat 160: 145-152, 2016.
5. Malmgren JA, Mayer M, Atwood MK and Kaplan HG: Differential presentation and survival of de novo and recurrent metastatic breast cancer over time: 1990-2010. Breast Cancer Res Treat 167: 579-590, 2018.
6. Tao L, Chu L, Wang LI, Moy L, Brammer M, Song C, Green M, Kurian AW, Gomez SL and Clarke CA: Occurrence and outcome of de novo metastatic breast cancer by subtype in a large, diverse population. Cancer Causes Control 27: 1127-1138, 2016.
7. Yoo TK, Chae BJ, Kim SJ, Lee J, Yoon TI, Lee SJ, Park HY, Park HK, Eom YH, Kim HS, *et al*: Identifying long-term survivors among metastatic breast cancer patients undergoing primary tumor surgery. Breast Cancer Res Treat 165: 109-118, 2017.
8. Lane WO, Thomas SM, Blitzblau RC, Plichta JK, Rosenberger LH, Fayanju OM, Hyslop T, Hwang ES and Greenup RA: Surgical resection of the primary tumor in women with de novo stage IV breast cancer: Contemporary practice patterns and survival analysis. Ann Surg 269: 537-544, 2019.
9. Bafford AC, Burstein HJ, Barkley CR, Smith BL, Lipsitz S, Iglehart JD, Winer EP and Golshan M: Breast surgery in stage IV breast cancer: Impact of staging and patient selection on overall survival. Breast Cancer Res Treat 115: 7-12, 2009.
10. Rapiti E, Verkooijen HM, Vlastos G, Fioretta G, Neyroud-Caspar I, Sappino AP, Chappuis PO and Bouchardy C: Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. J Clin Oncol 24: 2743-2749, 2006.
11. Babiera GV, Rao R, Feng L, Meric-Bernstam F, Kuerer HM, Singletary SE, Hunt KK, Ross MI, Gwyn KM, Feig BW, *et al*: Effect of primary tumor extirpation in breast cancer patients who present with stage IV disease and an intact primary tumor. Ann Surg Oncol 13: 776-782, 2006.

12. Gnerlich J, Jeffe DB, Deshpande AD, Beers C, Zander C and Margenthaler JA: Surgical removal of the primary tumor increases overall survival in patients with metastatic breast cancer: Analysis of the 1988-2003 SEER data. Ann Surg Oncol 14: 2187-2194, 2007.
13. Fields RC, Jeffe DB, Trinkaus K, Zhang Q, Arthur C, Aft R, Dietz JR, Eberlein TJ, Gillanders WE and Margenthaler JA: Surgical resection of the primary tumor is associated with increased long-term survival in patients with stage IV breast cancer after controlling for site of metastasis. Ann Surg Oncol 14: 3345-3351, 2007.
14. Bhoo-Pathy N, Verkooijen HM, Tan EY, Miao H, Taib NA, Brand JS, Dent RA, See MH, Subramaniam S, Chan P, *et al*: Trends in presentation, management and survival of patients with de novo metastatic breast cancer in a Southeast Asian setting. Sci Rep 5: 16252, 2015.
15. Pons-Tostivint E, Alouani E, Kirova Y, Dalenc F and Vaysse C: 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. Crit Rev Oncol Hematol 157: 103146, 2021.
16. Pons-Tostivint E, Kirova Y, Lusque A, Campone M, Geffrelot J, Mazouni C, Mailliez A, Pasquier D, Madranges N, Firmin N, *et al*: Survival impact of locoregional treatment of the primary tumor in de novo metastatic breast cancers in a large multicentric cohort study: A propensity score-matched analysis. Ann Surg Oncol 26: 356-365, 2019.
17. Soran A, Ozmen V, Ozbas S, Karanlik H, Muslumanoglu M, Igci A, Canturk Z, Utkan Z, Ozaslan C, Evrensel T, *et al*: Randomized trial comparing resection of primary tumor with no surgery in stage IV breast cancer at presentation: Protocol MF07-01. Ann Surg Oncol 25: 3141-3149, 2018.
18. Fitzal F, Bjelic-Radisic V, Knauer M, Steger G, Hubalek M, Balic M, Singer C, Bartsch R, Schrenk P, Soelkner L, *et al*: Impact of breast surgery in primary metastasized breast cancer: Outcomes of the prospective randomized phase III ABCSG-28 POSYTIVE trial. Ann Surg 269: 1163-1169, 2019.
19. Badwe R, Hawaldar R, Nair N, Kaushik R, Parmar V, Siddique S, Budrukkar A, Mittra I and Gupta S: Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: An open-label randomised controlled trial. Lancet Oncol 16: 1380-1388, 2015.
20. Harris E, Barry M and Kell MR: Meta-analysis to determine if surgical resection of the primary tumour in the setting of stage IV breast cancer impacts on survival. Ann Surg Oncol 20: 2828-2834, 2013.
21. Petrelli F and Barni S: Surgery of primary tumors in stage IV breast cancer: An updated meta-analysis of published studies with meta-regression. Med Oncol 29: 3282-3290, 2012.
22. Xiao W, Zou Y, Zheng S, Hu X, Liu P, Xie X, Yu P, Tang H and Xie X: Primary tumor resection in stage IV breast cancer: A systematic review and meta-analysis. Eur J Surg Oncol 44: 1504-1512, 2018.
23. Headon H, Wazir U, Kasem A and Mokbel K: Surgical treatment of the primary tumour improves the overall survival in patients with metastatic breast cancer: A systematic review and meta-analysis. Mol Clin Oncol 4: 863-867, 2016.
24. Gera R, Chehade HELH, Wazir U, Tayeh S, Kasem A and Mokbel K: Locoregional therapy of the primary tumour in de novo stage IV breast cancer in 216 066 patients: A meta-analysis. Sci Rep 10: 2952, 2020.
25. Arciero C, Liu Y, Gillespie T and Subhedar P: Surgery and survival in patients with stage IV breast cancer. Breast J 25: 644-653, 2019.
26. Cortesi L, Toss A, Cirilli C, Marcheselli L, Braghiroli B, Sebastiani F and Federico M: Twenty-years experience with de novo metastatic breast cancer. Int J Cancer 137: 1417-1426, 2015.
27. Zhao W, Wu L, Zhao A, Zhang M, Tian Q, Shen Y, Wang F, Wang B, Wang L, Chen L, *et al*: A nomogram for predicting survival in patients with de novo metastatic breast cancer: A population-based study. BMC Cancer 20: 982, 2020.
28. Di Meglio A, Freedman RA, Lin NU, Barry WT, Metzger-Filho O, Keating NL, King TA, Sertoli MR, Boccardo F, Winer EP and Vaz-Luis I: Time trends in incidence rates and survival of newly diagnosed stage IV breast cancer by tumor histology: A population-based analysis. Breast Cancer Res Treat 157: 587-596, 2016.
29. Bitencourt A, Rossi Saccarelli C, Morris EA, Flynn J, Zhang Z, Khan A, Gillespie E, Cahlon O, Mueller B, Cuaron JJ, *et al*: Regional lymph node involvement among patients with de novo metastatic breast cancer. JAMA Netw Open 3: e2018790, 2020.
30. Shen T, Siegal GP and Wei S: Clinicopathologic factors associated with de novo metastatic breast cancer. Pathol Res Pract 212: 1167-1173, 2016.
31. Shen T, Gao C, Zhang K, Siegal GP and Wei S: Prognostic outcomes in advanced breast cancer: The metastasis-free interval is important. Hum Pathol 70: 70-76, 2017.
32. Lobbezoo DJA, van Kampen RJW, Voogd AC, Dercksen MW, van den Berkmortel F, Smilde TJ, van de Wouw AJ, Peters FP, van Riel JMGH, Peters NAJB, *et al*: Prognosis of metastatic breast cancer: Are there differences between patients with de novo and recurrent metastatic breast cancer? Br J Cancer 112: 1445-1251, 2015.
33. Dawood S, Broglio K, Ensor J, Hortobagyi GN and Giordano SH: Survival differences among women with de novo stage IV and relapsed breast cancer. Ann Oncol 21: 2169-2174, 2010.
34. Yardley DA, Kaufman PA, Brufsky A, Yood MU, Rugo H, Mayer M, Quah C, Yoo B and Tripathy D: Treatment patterns and clinical outcomes for patients with de novo versus recurrent HER2-positive metastatic breast cancer. Breast Cancer Res Treat 145: 725-734, 2014.
35. Lao C, Kuper-Hommel M, Elwood M, Campbell I, Edwards M and Lawrenson R: Characteristics and survival of de novo and recurrent metastatic breast cancer in New Zealand. Breast Cancer 28: 387-397, 2021.
36. den Brok WD, Speers CH, Gondara L, Baxter E, Tyldesley SK and Lohrisch CA: Survival with metastatic breast cancer based on initial presentation, de novo versus relapsed. Breast Cancer Res Treat 161: 549-556, 2017.
37. Nieder C, Mannsåker B and Haukland E: Exceptional responses to standard therapy in a patient with metastatic HER2-positive breast cancer. Cureus 9: e1412, 2017.
38. Gobbini E, Ezzalfani M, Dieras V, Bachelot T, Brain E, Debled M, Jacot W, Mouret-Reynier MA, Goncalves A, Dalenc F, *et al*: Time trends of overall survival among metastatic breast cancer patients in the real-life ESME cohort. Eur J Cancer 96: 17-24, 2018.
39. Elbaiomy MA, Akl T, Atwan N, Elsayed AA, Elzaafarany M and Shamaa S: Clinical impact of breast cancer stem cells in metastatic breast cancer patients. J Oncol 2020: 2561726, 2020.
40. Dawood S, Haaland B, Albaracin C, Gupta S, Cortes J, Sim YY and Dent RA: Is the proportion of patients diagnosed with synchronous stage IV breast cancer who survive more than two years increasing over time? Oncology 89: 79-87, 2015.
41. Ogiya R, Sagara Y, Niikura N and Freedman RA: Impact of subtype on survival of young patients with stage IV breast cancer. Clin Breast Cancer 19: 200-207.e1, 2019.
42. Vaz-Luis I, Lin NU, Keating NL, Barry WT, Winer EP and Freedman RA: Factors associated with early mortality among patients with de novo metastatic breast cancer: A population-based study. Oncologist 22: 386-393, 2017.
43. Chen H, Zhang M, Wang M, Zhang P, Bai F and Wu K: Immediate breast reconstruction in de novo metastatic breast cancer: An analysis of 563 cases based on the SEER database. Clin Breast Cancer 19: e135-e141, 2019.
44. Khan SA, Stewart AK and Morrow M: Does aggressive local therapy improve survival in metastatic breast cancer? Surgery 132: 620-627, 2002.
45. Soares LR, Freitas-Junior R, Curado MP, Paulinelli RR, Martins E and Oliveira JC: Low overall survival in women with de novo metastatic breast cancer: Does this reflect tumor biology or a lack of access to health care? JCO Glob Oncol 6: 679-687, 2020.
46. Blanchard DK, Shetty PB, Hilsenbeck SG and Elledge RM: Association of surgery with improved survival in stage IV breast cancer patients. Ann Surg 247: 732-738, 2008.
47. King TA, Lyman JP, Gonen M, Voci A, De Brot M, Boafo C, Sing AP, Hwang ES, Alvarado MD, Liu MC, *et al*: Prognostic impact of 21-gene recurrence score in patients with stage IV breast cancer: TBCRC 013. J Clin Oncol 34: 2359-2365, 2016.
48. Carmichael AR, Anderson EDC, Chetty U and Dixon JM: Does local surgery have a role in the management of stage IV breast cancer? Eur J Surg Oncol 29: 17-19, 2003.
49. Lin C, Wu J, Ding S, Goh C, Andriani L, Lu S, Shen K and Zhu L: Subdivision of M1 stage for de novo metastatic breast cancer to better predict prognosis and response to primary tumor surgery. J Natl Compr Canc Netw 17: 1521-1528, 2019.

50. Plichta JK, Thomas SM, Sergesketter AR, Greenup RA, Rosenberger LH, Fayanju OM, Kimmick G, Force J, Hyslop T and Hwang ES: A novel staging system for de novo metastatic breast cancer refines prognostic estimates. Ann Surg 275: 784-792, 2022.
51. Garrido-Castro AC, Spurr LF, Hughes ME, Li YY, Cherniack AD, Kumari P, Lloyd MR, Bychkovsky B, Barroso-Sousa R, Di Lascio S, *et al*: Genomic characterization of de novo metastatic breast cancer. Clin Cancer Res 27: 1105-1118, 2021.
52. Seltzer S, Corrigan M and O'Reilly S: The clinicomolecular landscape of de novo versus relapsed stage IV metastatic breast cancer. Exp Mol Pathol 114: 104404, 2020.
53. McKenzie HS, Maishman T, Simmonds P, Durcan L; POSH Steering Group; Eccles D and Copson E: Survival and disease characteristics of de novo versus recurrent metastatic breast cancer in a cohort of young patients. Br J Cancer 122: 1618-1629, 2020.
54. Di Meglio A, Lin NU, Freedman RA, Barry WT, Winer EP and Vaz-Luis I: Patterns of utilization of imaging studies and serum tumor markers among patients with de novo metastatic breast cancer. J Natl Compr Canc Netw 15: 316-324, 2017.
55. Shien T, Kinoshita T, Shimizu C, Hojo T, Taira N, Doihara H and Akashi-Tanaka S: Primary tumor resection improves the survival of younger patients with metastatic breast cancer. Oncol Rep 21: 827-832, 2009.
56. Barinoff J, Schmidt M, Schneeweiss A, Schoenegg W, Thill M, Keitel S, Lattrich CR, Hinke A, Kutscheidt A and Jackisch C: Primary metastatic breast cancer in the era of targeted therapy-prognostic impact and the role of breast tumour surgery. Eur J Cancer 83: 116-124, 2017.
57. Co M, Ng J and Kwong A: De-novo metastatic breast cancers with or without primary tumor resection-A 10-year study. Cancer Treat Res Commun 19: 100118, 2019.
58. Kwong A and Co M: Long term survival study of de-novo metastatic breast cancers with or without primary tumour resection. Cancer Treat Res Commun 20: 100148, 2019.
59. Rao R, Feng L, Kuerer HM, Singletary SE, Bedrosian I, Hunt KK, Ross MI, Hortobagyi GN, Feig BW, Ames FC and Babiera GV: Timing of surgical intervention for the intact primary in stage IV breast cancer patients. Ann Surg Oncol 15: 1696-1702, 2008.
60. Cady B, Nathan NR, Michaelson JS, Golshan M and Smith BL: Matched pair analyses of stage IV breast cancer with or without resection of primary breast site. Ann Surg Oncol 15: 3384-3395, 2008.
61. Soran A, Özbaş S, Doğan L, Sezgin E, Özmen V, Beriwal S and Brufsky A: Loco-regional treatment for intact primary tumor in patient with de novo metastatic breast cancer; comments and concerns of ECOG-ACRIN 2108 trial. Eur J Breast Health 16: 158-159, 2020.
62. Poggio F, Lambertini M and de Azambuja E: Surgery of the primary tumour in patients presenting with de novo metastatic breast cancer: to do or not to do? ESMO Open 3: e000324, 2018.
63. Teshome M: Role of operative management in stage IV breast cancer. Surg Clin North Am 98: 859-868, 2018.
64. Altundag K: Questions about the primary tumor resection for de-novo metastatic breast cancers. Cancer Treat Res Commun 20: 100131, 2019.
65. Altundag K: Predictive role of loco-regional radiotherapy among metastatic breast cancer patients who had undergone primary tumor surgery. Breast Cancer Res Treat 167: 303, 2018.
66. Gultekin M, Yazici O, Eren G, Yuce D, Aksoy S, Ozisik Y, Guler N, Yazici G, Hurmuz P, Yildiz F, *et al*: Impact of locoregional treatment on survival in patients presented with metastatic breast carcinoma. Breast 23: 775-783, 2014.
67. Kim YJ, Jung SY and Kim K: Survival benefit of radiotherapy after surgery in de novo stage IV breast cancer: A population-based propensity-score matched analysis. Sci Rep 9: 8527, 2019.
68. Tan Y, Li X, Chen H, Hu Y, Jiang M, Fu J, Yuan Y and Ding K: Hormone receptor status may impact the survival benefit of surgery in stage IV breast cancer: A population-based study. Oncotarget 7: 70991-71000, 2016.
69. Wang K, Shi Y, Li ZY, Xiao YL, Li J, Zhang X and Li HY: Metastatic pattern discriminates survival benefit of primary surgery for de novo stage IV breast cancer: A real-world observational study. Eur J Surg Oncol 45: 1364-1372, 2019.
70. Samiee S, Berardi P, Bouganim N, Vandermeer L, Arnaout A, Dent S, Mirsky D, Chasen M, Caudrelier JM and Clemons M: Excision of the primary tumour in patients with metastatic breast cancer: A clinical dilemma. Curr Oncol 19: e270-e279, 2012.
71. Rashaan ZM, Bastiaannet E, Portielje JE, van de Water W, van der Velde S, Ernst MF, van de Velde CJ and Liefers GJ: Surgery in metastatic breast cancer: Patients with a favorable profile seem to have the most benefit from surgery. Eur J Surg Oncol 38: 52-56, 2012.
72. Retsky M, Bonadonna G, Demicheli R, Folkman J, Hrushesky W and Valagussa P: Hypothesis: Induced angiogenesis after surgery in premenopausal node-positive breast cancer patients is a major underlying reason why adjuvant chemotherapy works particularly well for those patients. Breast Cancer Res 6: R372-E374, 2004.
73. Hofer SO, Molema G, Hermens RA, Wanebo HJ, Reichner JS and Hoekstra HJ: The effect of surgical wounding on tumour development. Eur J Surg Oncol 25: 231-243, 1999.
74. O'Reilly MS, Holmgren L, Shing Y, Chen C, Rosenthal RA, Moses M, Lane WS, Cao Y, Sage EH and Folkman J: Angiostatin: A novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma. Cell 79: 315-328, 1994.
75. Gunduz N, Fisher B and Saffer EA: Effect of surgical removal on the growth and kinetics of residual tumor. Cancer Res 39: 3861-3865, 1979.
76. Rashid OM and Takabe K: Does removal of the primary tumor in metastatic breast cancer improve survival? J Womens Health (Larchmt) 23: 184-188, 2014.
77. Cacho-Díaz B, García-Botello DR, Wegman-Ostrosky T, Reyes-Soto G, Ortiz-Sánchez E and Herrera-Montalvo LA: Tumor microenvironment differences between primary tumor and brain metastases. J Transl Med 18: 1, 2020.
78. Khodari W, Sedrati A, Naisse I, Bosc R and Belkacemi Y; AROME (Association of Radiotherapy and Oncology of the Mediterranean arEa; www.aromecancer.org): Impact of loco-regional treatment on metastatic breast cancer outcome: A review. Crit Rev Oncol Hematol 87: 69-79, 2013.
79. Karnoub AE, Dash AB, Vo AP, Sullivan A, Brooks MW, Bell GW, Richardson AL, Polyak K, Tubo R and Weinberg RA: Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. Nature 449: 557-563, 2007.
80. Trovato R, Canè S, Petrova V, Sartoris S, Ugel S and De Sanctis F: The engagement between MDSCs and metastases: Partners in crime. Front Oncol 10: 165, 2020.
81. Moserle L, Amadori A and Indraccolo S: The angiogenic switch: Implications in the regulation of tumor dormancy. Curr Mol Med 9: 935-941, 2009.
82. Kazerounian S and Lawler J: Integration of pro- and anti-angiogenic signals by endothelial cells. J Cell Commun Signal 12: 171-179, 2018.
83. Kozłowski J, Kozłowska A and Kocki J: Breast cancer metastasis-insight into selected molecular mechanisms of the phenomenon. Postepy Hig Med Dosw (Online) 69: 447-451, 2015.
84. Nguyen DH and Truong PT: A debate on locoregional treatment of the primary tumor in patients presenting with stage IV breast cancer. Expert Rev Anticancer Ther 11: 1913-1922, 2011.
85. Pantel K and Speicher MR: The biology of circulating tumor cells. Oncogene 35: 1216-1224, 2016.
86. Wang WC, Zhang XF, Peng J, Li XF, Wang AL, Bie YQ, Shi LH, Lin MB and Zhang XF: Survival mechanisms and influence factors of circulating tumor cells. Biomed Res Int 2018: 6304701, 2018.
87. Becker A, Thakur BK, Weiss JM, Kim HS, Peinado H and Lyden D: Extracellular vesicles in cancer: Cell-to-cell mediators of metastasis. Cancer Cell 30: 836-848, 2016.
88. Dos Anjos Pultz B, Andrés Cordero da Luz F, Socorro Faria S, Peixoto Ferreira de Souza L, Cristina Brígido Tavares P, Alonso Goulart V, Fontes W, Ricardo Goulart L and José Barbosa Silva M: The multifaceted role of extracellular vesicles in metastasis: Priming the soil for seeding. Int J Cancer 140: 2397-2407, 2017.
89. Wortzel I, Dror S, Kenific CM and Lyden D: Exosome-mediated metastasis: Communication from a distance. Dev Cell 49: 347-360, 2019.
90. Wong CC, Gilkes DM, Zhang H, Chen J, Wei H, Chaturvedi P, Fraley SI, Wong CM, Khoo US, Ng IO, *et al*: Hypoxia-inducible factor 1 is a master regulator of breast cancer metastatic niche formation. Proc Natl Acad Sci USA 108: 16369-16374, 2011.
91. Noguchi M, Nakano Y, Noguchi M, Ohno Y and Kosaka T: Local therapy and survival in breast cancer with distant metastases. J Surg Oncol 105: 104-110, 2012.
92. Yousefi M, Nosrati R, Salmaninejad A, Dehghani S, Shahryari A and Saberi A: Organ-specific metastasis of breast cancer: Molecular and cellular mechanisms underlying lung metastasis. Cell Oncol (Dordr) 41: 123-140, 2018.

93. Sun S and Qiu XS: Cancer stem cells and tumor metastasis. J Cancer Res Ther 9 (Suppl): S150-S152, 2013.
94. Marcuzzi E, Angioni R, Molon B and Calì B: chemokines and chemokine receptors: Orchestrating tumor metastasization. Int J Mol Sci 20: 96, 2018.
95. O'Hayre M, Salanga CL, Handel TM and Allen SJ: Chemokines and cancer: Migration, intracellular signalling and intercellular communication in the microenvironment. Biochem J 409: 635-649, 2008.
96. Ma R, Feng Y, Lin S, Chen J, Lin H, Liang X, Zheng H and Cai X: Mechanisms involved in breast cancer liver metastasis. J Transl Med 13: 64, 2015.
97. Seguin L, Desgrosellier JS, Weis SM and Cheresh DA: Integrins and cancer: Regulators of cancer stemness, metastasis, and drug resistance. Trends Cell Biol 25: 234-240, 2015.
98. Naxerova K and Jain RK: Using tumour phylogenetics to identify the roots of metastasis in humans. Nat Rev Clin Oncol 12: 258-272, 2015.
99. Norton L and Massagué J: Is cancer a disease of self-seeding? Nat Med 12: 875-878, 2006.
100. Danna EA, Sinha P, Gilbert M, Clements VK, Pulaski BA and Ostrand-Rosenberg S: Surgical removal of primary tumor reverses tumor-induced immunosuppression despite the presence of metastatic disease. Cancer Res 64: 2205-2211, 2004.
101. Criscitiello C, Giuliano M, Curigliano G, De Laurentiis M, Arpino G, Carlomagno N, De Placido S, Golshan M and Santangelo M: Surgery of the primary tumor in de novo metastatic breast cancer: To do or not to do? Eur J Surg Oncol 41: 1288-1292, 2015.
102. Jiang ZF, Cristofanilli M, Shao ZM, Tong ZS, Song EW, Wang XJ, Liao N, Hu XC, Liu Y, Wang Y, *et al*: Circulating tumor cells predict progression-free and overall survival in Chinese patients with metastatic breast cancer, HER2-positive or triple-negative (CBCSG004): A multicenter, double-blind, prospective trial. Ann Oncol 24: 2766-2772, 2013.
103. Cristofanilli M, Budd GT, Ellis MJ, Stopeck A, Matera J, Miller MC, Reuben JM, Doyle GV, Allard WJ, Terstappen LWMM and Hayes DF: Circulating tumor cells, disease progression, and survival in metastatic breast cancer. N Engl J Med 351: 781-791, 2004.
104. Hazard HW, Gorla SR, Scholtens D, Kiel K, Gradishar WJ and Khan SA: Surgical resection of the primary tumor, chest wall control, and survival in women with metastatic breast cancer. Cancer 113: 2011-2019, 2008.
105. Dauplat J, Le Bouëdec G, Pomel C and Scherer C: Cytoreductive surgery for advanced stages of ovarian cancer. Semin Surg Oncol 19: 42-48, 2000.
106. Dooley WC: A surgical indication in incurable breast cancer. Ann Surg Oncol 13: 759-760, 2006.
107. Ruiterkamp J, Ernst MF, van de Poll-Franse LV, Bosscha K, Tjan-Heijnen VC and Voogd AC: Surgical resection of the primary tumour is associated with improved survival in patients with distant metastatic breast cancer at diagnosis. Eur J Surg Oncol 35: 1146-1151, 2009.
108. Leung AM, Vu HN, Nguyen KA, Thacker LR and Bear HD: Effects of surgical excision on survival of patients with stage IV breast cancer. J Surg Res 161: 83-88, 2010.
109. Pathy NB, Verkooijen HM, Taib NA, Hartman M and Yip CH: Impact of breast surgery on survival in women presenting with metastatic breast cancer. Br J Surg 98: 1566-1572, 2011.
110. Bertaut A, Mounier M, Desmoulins I, Guiu S, Beltjens F, Darut-Jouve A, Ponnelle T, Arnould L and Arveux P: Stage IV breast cancer: A population-based study about prognostic factors according to HER2 and HR status. Eur J Cancer Care (Engl) 24: 920-928, 2015.
111. Lopez-Tarruella S, Escudero MJ, Pollan M, Martín M, Jara C, Bermejo B, Guerrero-Zotano A, García-Saenz J, Santaballa A, Alba E, *et al*: Survival impact of primary tumor resection in de novo metastatic breast cancer patients (GEICAM/El Alamo Registry). Sci Rep 9: 20081, 2019.
112. Pons-Tostivint E, Kirova Y, Lusque A, Campone M, Geffrelot J, Rivera S, Mailliez A, Pasquier D, Madranges N, Firmin N, *et al*: Radiation therapy to the primary tumor for de novo metastatic breast cancer and overall survival in a retrospective multicenter cohort analysis. Radiother Oncol 145: 109-116, 2020.
113. Rosche M, Regierer AC, Schwarzlose-Schwarck S, Weigel A, Bangemann N, Schefe JH, Scholz CW, Possinger K and Eucker J: Primary tumor excision in stage IV breast cancer at diagnosis without influence on survival: A retrospective analysis and review of the literature. Onkologie 34: 607-612, 2011.