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REVIEW

HR+/HER2- de novo metastatic breast cancer: a true peculiar entity?

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Abstract

De novo metastatic breast cancer (dnMBC) accounts for ~6–10% of all breast cancers and for ~30% of MBC with increasing incidence over time. Hormone receptor-positive/human epidermal growth factor receptor 2-negative ($HR^+/HER2^-$) tumours are the most frequent subtype with a similar incidence to that observed amongst recurrent MBC (rMBC). Higher frequency of *PI3KCA* and *ARID2* mutations and a lower frequency of *ESR1* mutations and of genes involved in DNA damage, as compared with rMBC, have been reported in $HR^+/HER2^-$ dnMBC; however, these are not correlating with prognosis, whilst tumour mutational burden is inversely correlated with outcome. Bone represents the most frequent metastatic site, being the single site in up to 60% of patients with dnMBC. $HR^+/HER2^-$ dnMBC has been generally reported to have better outcomes than rMBC, with a median overall survival ranging from 26 months to nearly 5 years in patients with favourable features such as age <40 years and bone-only disease, but not when compared with patients with late recurring disease (≥2–5 years). Analyses of the de novo cohorts within randomized clinical trials and large real-world series report a better outcome after treatment with CDK4/6 inhibitors and endocrine agents as compared to rMBC. Despite the limitations of retrospective studies and controversial results of the randomized trials, locoregional treatment of the primary tumour after response to systemic therapy appears to confer a survival benefit, particularly in patients with favourable prognostic factors. Altogether genomic, biological and clinical findings highlight $HR^+/HER2^-$ dnMBC as a peculiar entity as compared with rMBC and deserve a dedicated treatment algorithm.

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Introduction

Approximately 6–10% of breast cancers have distant metastases at diagnosis and are defined as de novo metastatic breast cancer (dnMBC).[1] dnMBC was formerly considered a marginal subset of MBC. In 2010, Dawood et al.[2] reported a large cohort study including 3524 patients diagnosed with MBC at the MD Anderson Cancer Center from 1992 to 2007. Patients with dnMBC represented 18.4% of the entire cohort and differentiated from those with recurrent disease by being older in age and with a higher proportion of hormone receptor-positive (HR^+) tumours. In addition, dnMBC was associated with improved overall survival (OS) and a lower risk of death, in particular in comparison with women who had recurrent MBC (rMBC) within 5 years from first diagnosis of breast cancer.

The decrease in rMBC due to earlier diagnosis and improvements in adjuvant treatments as well as the steady incidence of dnMBC observed in the past decades have led to the relative increase in the proportion of dnMBC which, according to recent large population registries, is approximately one-third of all MBC and is expected to grow over time.[3–5] On the other hand, 5-year disease-specific survival of dnMBC has improved over time, from 28% to 55%, whereas that of rMBC has worsened, from 23% to 13%.[3] This opposite trend has fuelled interest in a deepened knowledge of epidemiology, biology and treatment outcomes of dnMBC contributing

to the appraisal of dnMBC as a distinct entity in the heterogeneous landscape of MBC. Subsequently, a growing number of prospective trials and retrospective series have reported outcomes for dnMBC separately.

This is a critical narrative review focusing on HR+/human epidermal growth factor receptor 2-negative (HER2-) dnMBC in terms of genomic, biological, pathological, and clinical features and outcomes after systemic and locoregional treatments, outlining differences with rMBC.

Methods

Articles were retrieved by searching PubMed full reports published from 2015 to November 2022. Primary key terms used for article retrieval were "de novo metastatic breast cancer" and "stage IV breast cancer". We included large series of dnMBC with or without comparison with rMBC reporting data for the HR+/HER2- subtype separately. We decided to include only reports with data collected from 2010 in order to have reliable information on HR and HER2 status and to consider the availability of more efficacious modern therapies.

Results

Epidemiology

Large institution series and population-based registries in western countries reported an incidence of dnMBC of up to 6%, whilst in low-income countries, such as Ethiopia and India, the incidence of dnMBC was reported to be of up to 30%.[1] This incidence has generally been reported to be steady over time, though a slight increase has been reported in the SEER database.[1,6] Analyses of demographic characteristics have indicated that black race, lower socioeconomic status, and rural residence are associated with a higher incidence of dnMBC, suggesting that populations with limited healthcare and screening programme access were more likely to be diagnosed with later-stage breast cancer.[1] This hypothesis may be supported by the increasing incidence at a steady rate over the last decades of dnMBC in young women (aged ≤40 years) who may benefit less from screening programmes. In contrast, other studies reported dnMBC to be significantly associated with older age, whilst being much rarer in women aged ≤40 years.[7] Other studies showing the prevalence of more aggressive subtypes in dnMBC as compared to rMBC have provided an alternative explanation for this slight but constant increase in dnMBC in western countries despite the general improvement in screening programmes, which are not capable of catching rapidly growing tumours.[6]

Therefore, questions arise regarding the reasons why some tumours spread to distant sites at the very beginning of their development, whilst others continue to grow only locally in the breast or in regional nodes. Moreover, it is poorly understood how tumours that arise with a greater disease burden often experience better prognosis.

Genomic landscape

It remains unclear whether genomic and biological features specific to dnMBC, with respect to rMBC, drive the earlier onset of metastatic disease in dnMBC and account for the differing prognosis.[8] Unravelling the genomic landscape of dnMBC may thus represent an opportunity to better elucidate the driving process of the metastatic spread and the net alterations occurring under treatment pressure.[8]

In 2012, The Cancer Genome Atlas first described the mutational landscape of breast cancer and highlighted that the most frequent mutations, occurring in at least 10% of samples, were *TP53*, *PI3KCA, GATA3* and *MAP3K1*. The samples examined in the study were mostly primary tumours.[9] Since then, several studies have investigated the genomic profile of MBC, reporting conflicting data on analogies and differences with primary tumours.[10–12] Despite differences in populations and in methodologies amongst studies, it seems likely that MBC genomic profiles differ from those of primary tumours, with tumour subtype-specific peculiarities.[11–13] Whether the differences are due to the selective pressures imposed by the metastatic process itself and the systemic therapies, or both, remain unclear.

Mutations of genes in the *P3KCA–AKT* pathway were the most frequently represented in both early and metastatic HR+ breast cancer, ranging from 35% to 40% in both groups; likewise, *TP53* and *GATA3* mutations were similarly distributed in primary breast cancer and MBC. On the other hand, *ESR1* mutations were detectable in 13–20% of MBC, particularly in endocrine-resistant tumours, whilst their occurrence was negligible in the early setting. Other common genomic alterations in HR+ breast cancer, including *CDH1*, *MAP3K1*, *MAP2K4*, *NF1* and *ERBB2*, were enriched in MBC and have been implicated as potential driver mutations and in mechanisms of endocrine resistance.[11,13]

Less evidence on the genomic profile of dnMBC is currently available. Seltzer et al. compared the clinicopathological and gene expression profiles of 17 dnMBC (10 HR+/HER2-) and 49 treatment-naive rMBC (39 HR+/HER2-) samples accessed from The Cancer Genome Atlas.[14] dnMBC were more likely to be HR+ and HER2+, to present at a higher stage (more T4 and node positive) and to be less histologically aggressive. Nevertheless, given the small sample size, genomic and clinical data were not reported by tumour subtype. *TP53* and *PI3KCA* were confirmed as the most frequent mutations in

both dnMBC and rMBC, whilst dnMBC were more likely to have *PTEN* (25% *versus* 6.1%) and *GATA3* (18.7% *versus* 10.2%) mutations. *TP53* and *PIK3CA* alterations showed no survival differences in either group, whilst alterations in *GATA3* and *ABL2* had poor survival outcomes for dnMBC but not for rMBC.[14] Altogether, the study outlined that dnMBC showed increased cytoskeletal regulation, was more steroid dependent, had decreased lymphocytic infiltrate and had downregulation of chemotaxis, whilst rMBC was more immunogenic, more likely to be triple negative (TN) and targeted the extracellular matrix more frequently.[14] Analysis of survival showed a significantly improved OS for dnMBC (36 *versus* 12 months; p=0.02), which was restricted to the comparison with the group of patients recurring <2 years, whilst no difference was observed in the comparison with patients with a metastasis-free interval (MFI) of >2 years.[14]

Garrido-Castro et al. reported the largest descriptive and comparative analysis of genomic profiles obtained by next-generation sequencing using 212 dnMBC and primary 714 tumours that recurred later.[8] Appropriately, the authors compared only primary tumours to avoid the potential bias of treatment-induced mutations in metastatic samples. Sixty-four percent of de novo tumours were HR+/HER2- tumours *versus* 47% of recurrent breast cancer, and 24% *versus* 11.2% were HER2+ amongst de novo and recurrent tumours, respectively, whilst TN tumours were more frequent amongst rMBC (21.6 *versus* 1.8% in dnMBC).[8] Overall, in HR+/HER2- tumours, the most frequently mutated genes were *PIK3CA* (41.9%) and *CDH1* (24.3%), whilst across all treatment-naive HR+/HER2- samples (105), only 3 (2.9%) activating *ESR1* mutations were identified. Comparison of genomic profiles indicated lower *TP53* (11% *versus* 25.1%) and higher *PI3KCA* (41.6% *versus* 29.8%) expression in dnMBC as compared with recurring tumours. FGFR amplification was observed in 14.7% and 10.8% of dnMBC and rMBC, whilst *CCND1* amplifications were similar in the two groups (17.6% and 16.6%).[8]

In HR+/HER2- tumours, greater prevalence of mutations in genes involved in epigenetic modulation, such as *KMT2D* and *SETD2*, were present in dnMBC *versus* stage I–III primary tumours (14.6% and 9% *versus* 6.0% and 2.1%, respectively). In contrast, proportionally significantly fewer mutations in genes involved in DNA damage, such as *TP53* and *BRCA1*, were observed in dnMBC (21.3% and 0 *versus* 32.3% and 7.7% in rMBC, respectively). When restricting the analysis to likely oncogenic mutations, only differences in *TP53* (11.2% *versus* 25.1%) and *PI3KCA* (41.6% *versus* 29.8%) were significant, suggesting the presence of a predominant luminal A-like phenotype in HR+/HER2- dnMBC compared with luminal B-like tumours in patients who developed rMBC. Moreover, the higher prevalence of *PIK3CA* mutations suggests a functional role for *PIK3CA* in mediating metastatic spread.[8]

Patients with dnMBC had a longer OS than those with rMBC (78.6 *versus* 59.9 months; p=0.0056), with particular benefit in the HR+/HER2- cohort but not in the TN subgroup. Amongst the former group, *TP53* mutations, alterations in mismatch repair genes, amplification of *MYC*, *Rad21* and *MYB*, and deletions of *CDKCDKN2A/CDKN2B* correlated with worse OS, whilst mutations in *KMT2D* predicted improved OS. In multivariate analysis after adjusting for tumour subtypes, all the above-mentioned alterations, except those of mismatch repair genes and mutations of *KMTD*, retained significance. In addition, *TP53* mutations were prognostic in both dnMBC and rMBC, whilst *MYC* amplifications, despite not differing between the two cohorts, were prognostic only in the former group.[8] Median tumour mutational burden (TMB) was 7.2 mut/kb in both groups and patients with HR+/HER2- tumours in the highest TMB quartile had numerically inferior OS, in contrast to observations in the TN cohort, where TMB positively correlated with OS.[8]

The Aiming to Understand the Molecular Aberrations in Metastatic Breast Cancer (AURORA) study is a prospective study ran by the Breast International Group that collected tissues from primary breast cancer along with paired metastasis and plasma samples obtained before treatment initiation with the aim of identifying molecular alterations enriched in the early phases of metastatic disease and of describing variations in gene expression between primary samples and their paired metastasis.[15] The analysis included 379 samples, with 65% consisting of HR+/HER2- tumours, amongst whom 41 patients had dnMBC. Overall, similar alterations were found in both primary dnMBC and non-de novo tumours, in contrast to metastatic tissues, where an enrichment in alterations, in particular *ESR1* mutations, was found in non-de novo tumours but not in dnMBC. However, the small number of patients in the dnMBC group did not allow firm conclusions to be drawn.[15] Despite a general large concordance in driver mutation prevalence between primary and metastatic samples (88%), gene expression differences between the two samples were significantly greater only in non-de novo HR+/HER2- versus de novo samples but not in the other subtypes. Moreover, greater gene expression differences in metastatic samples were associated with a longer time to relapse.[15] Overall, the median TMB in dnMBC was significantly lower than in rMBC (p=−0.46) and, in HR+/HER2- tumours, it was lower in primary tumours than in metastatic samples and was a negative independent prognostic factor.[15]

In a prospective analysis of paired primary and metastatic tumours, in the small number (n=11) of dnMBC samples, including only 3 HR+/HER2- tumours a divergent phenotype between primary and metastasis was observed only in 1 case. In addition, synchronous metastases had a significantly lower number of metastasis-

specific mutations as compared with metachronous metastases.[16] The small sample size prevented a separate analysis for luminal tumours, but these data support a greater genomic similarity in dnMBC than in rMBC between primary and metastatic sites.[16]

In a recent meta-analysis of data sequencing of 4268 MBC (728 of which were HR+/HER2-, 86 dnMBC) and 5217 (618 of which were HR+/HER2-) unpaired primary breast cancer samples from eight different cohorts, no difference was observed in the frequency of the most represented genetic alterations in MBC, compared with that in primary samples, except for *ESR1*, *ARID1A* and *NF1*, which were more frequently altered in the former group, *ESR1* mutations having the highest frequency in post-treatment MBC samples.[17] On the other hand, only alterations in *ARID2* were more frequent in dnMBC as compared with primary breast cancer, independently of tumour subtype.[17] An analysis of mutations according to the metastatic site showed that, whilst in rMBC *ESR1* mutations were prevalent in liver mutations, *RICTOR* mutations were prevalent in bone metastases and were also frequently observed in HR+/HER2- de novo treatment-naive MBC.[17]

Despite the above-mentioned genomic and molecular analysis of cohorts of both dnMBC and rMBC, whether differences in tumour biology between dnMBC and rMBC drive the earlier onset of metastatic disease in dnMBC and whether there are intrinsic genomic features in dnMBC that confer a survival advantage compared with rMBC remain unresolved issues.

Clinical presentation and outcome

A growing amount of data on clinical features and outcome of dnMBC have been obtained by several studies in different time spans of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, using the 18-registry database, which collects cancer incidence and survival data from 18 population-based cancer registries covering about 30% of the US population.[6,18–27] Data were also extracted from other national or regional registries such as the California Cancer registry,[28] the Netherlands Cancer Registry,[29] the Cote d'Or Registry in France,[30] Sweden,[31] Modena Registry in Italy[32] and New Zealand Cancer Registry,[33] as well as from national databases such as the National Cancer database in the USA,[34] the Epidemiological Strategy and Medical Economics (ESME) in France[5,35,36] and the British Columbia Cancer Agency.[37] In addition, multicentric or large, single institution series have been reported from MD Anderson Cancer Center[38] and academic institutions from the USA,[3,39] Netherlands,[40] Japan[41] and China.[42] Of note, the definition of dnMBC slightly varied amongst series, including tumours with metastases discovered at the same time or within 3–6 months from breast cancer diagnosis.

HR+/HER2- is by far the most frequent subtype amongst dnMBC, reaching 60% of cases in most series, despite conflicting data on incidence, as compared with rMBC, whilst HER2+ tumours, which mostly occur at a higher incidence in the de novo cohort and TN tumours, are definitely less frequently represented amongst dnMBC.[3,30,33,37]

HR+/HER2- dnMBC generally presents with a greater tumour size and nodal involvement as compared with rMBC,[6,14,28,37,40] whilst a higher incidence of grade 3 tumours has not been confirmed in all series.[3,6,14,22,23,26,30,37,40,41] Moreover, lobular histology is relatively less frequent amongst dnMBC[14,30,43] and patients with dnMBC are generally reported to be older than those with rMBC.[14,26,37,39,43]

About 30% of HR+/HER2- dnMBC presented with multiple metastatic sites, similarly to what is reported for rMBC,[30,44] and bone represented the preferred site of metastatic spread in either dnMBC and rMBC, ranging from 25% to 64%.[6,18,19,40,41,43–45] HR+/HER2- dnMBC presented with bone-only disease more frequently than other subtypes, ranging from 20% to 60%.[18,19,22,23,44,45] Visceral metastases overall were similarly reported,[3,40] whilst brain metastases, albeit rare in the luminal subtype, were more frequent in rMBC.[3,40]

Comparing metastatic pattern amongst subtypes, bone remained the preferred site for all subtypes but was more often the single metastatic site in luminal tumours,[23,24] whilst liver and brain metastases were definitely more frequent in HER2+ and TN tumours.[18,22–24] Lung was generally the most common visceral metastatic site in HR+/HER2- tumours, being reported in >20% of cases, but data on relative incidence with other subtypes are inconsistent.[18,22,23,41] On the contrary, in a small series from the Alabama Tumor Registry, a trend in favour of rMBC for a single metastatic site was reported (75% *versus* 67% in dnMBC) and bone was the preferred site only in HR+/HER2- dnMBC whilst liver was more frequent in HER+ tumours and lung in TN.[43] A retrospective study from MD Anderson Cancer Center failed to find a significant correlation between mutational profile and metastatic pattern, though a prevalence of *PI3KCA* mutations was observed in bone-only metastatic tumours.[45]

When clinical features of rMBC were split according to MFI, the incidence of luminal A tumours grew along with time to recurrence, particularly after 5 years or more.[33] In addition, early rMBC presented significantly more visceral and brain metastases as compared with dnMBC and late rMBC,[33,40] though the number of metastatic sites was not different.[33] Since the seminal report of the MD Anderson series, showing a 12-month improvement in median OS (mOS) for patients diagnosed with stage IV breast cancer as compared with rMBC, dnMBC has

generally been considered to lead to a better prognosis.[2] The MD Anderson study did not show results according to tumour subtype, though HR+/HER2+ tumours led to a significantly longer survival (41.4 and 45.9 months, respectively).[2]

In subsequent studies reporting outcomes for the HR+/HER2- subtype (Table 1), mOS ranged from 26 months to nearly 5 years in patients with particularly favourable prognostic features, such as young age and bone-only disease, but was generally lower than that of HR+/HER2+ dnMBC,[5,18,19,24,25,34,38,46] though this difference was not statistically different in all series and even favours the former subtype in some small series.[28,29,42]

Patients with HR+/HER2+ tumours maintained an improved OS even if the proportion of patients with bone-only disease, a known favourable prognostic factor, was generally much higher in patients with HR+/HER2- tumours.[18,19,39] Breast cancer specific survival was also reported to be higher in patients with HR+/HER2+ breast cancer (from 44 months to 72 months) than in those with HR+/HER2-

Table 1. Studies reporting outcomes of HR+/HER2- dnMBC cohorts.

Author (year)	Source	MBC/ dnMBC	dnMBC HR+/ HER2- (%)	OS months (median)	rMBC HR/ HER2- (%)	OS months (median)
Taskindoust (2021)[25]	SEER 2010–2016	19,444	62.4	33	–	–
den Brok (2017)[37]	BCCA DB 2001–2009	2085/711	57.1	34	56.3	23
Marshall (2017)[30]	Cote d'Or Registry 2000–2011	622/254	68.5	25.9	23.8	–
Tao (2016)[28]	California Cancer Registry 2005–2011	6268/2738	43.7	38	–	–
Yamamura (2018)[41]	Medical Center Japan 2000–2013	172/65	–	4.85[a]	–	3.15
Li (2020)	SEER 2012–2016[b]	3384	63.4	39	–	–
Zhang (2020)[23]	University Hospital Registry Tianjin 2008–2016	1890/171	56.7	41	–	–
Lao (2021)[33]	New Zealand Breast Cancer Registry 2010–2017	2167/667	49	41 (Lum A) 16 (Lum B)	52	23 (Lum A) 11 (Lum B)
Mallet (2022)[36]	National Population Registry 2008–2016	22,109/4254	63	58.5/52.3[c]	–	–
Ogiya (2019)[21]	SEER 2010–2014	6302	49	45/39[c]	–	–
Leone (2021)[53]	SEER 2010–2017	250	57.2	33	–	–
File (2022)[39]	UNC MBC Database 2011–2017	844/232	50	42.1	52.4	35.2
Sun (2022)[27]	SEER 2010–2108	1675 ILC	88	34[e]	–	–

[a]Years.
[b]Patients with bone-only metastasis.
[c]OS of patients with dnMBC aged <40 years and 40–59 years.
[d]Population of male patients.
[e]Not stratified by subtype.
BCCA, British Columbia Cancer Agency; dnMBC, de novo metastatic breast cancer; ILC, invasive lobular cancer; Lum, luminal; MBC, metastatic breast cancer; OS, overall survival; rMBC, recurrent metastatic breast cancer; SEER, Surveillance, Epidemiology, and End Results; UNC, University of North Carolina.

tumours (50 and 20 months; in moderate and poorly differentiated tumours, respectively).[47]

Importantly, in a large series of nearly 20,000 patients with dnMBC diagnosed from 2010 to 2016 in the SEER database, patients with HR+/HER2- tumours were amongst those who had an increased likelihood of dying for non-cancer-related causes as were those with HER+ tumours and a single metastatic site, particularly bone.[25]

Comparisons of prognosis with rMBC showed conflicting results, with the majority but not all studies showing an improved OS for dnMBC (Table 1). However, when prognosis of rMBC was split according to MFI, earlier recurrence (mainly <2 years and 3 years[39]) was generally associated, as expected, with poorer prognosis, though not in all studies. Conversely, most series did not report different survival between patients with dnMBC and those with rMBC, with a longer MFI despite different cut off for this definition (from >2 to 5 years).[37,39–41,43] Finally, a 5-year survival exceeding 30% has been reported in some series of HR+/HER2- dnMBC.[23,33,39]

Special populations

Young women (age ≤40 years)

dnMBC represents 1–7% of all MBC diagnosed in women aged ≤40 years.[7] Conflicting evidence on the relative incidence of dnMBC amongst young women as compared with older women is available.[7] In HR+/HER2- tumours, age-related genomic differences have been reported, with young women showing features of increased endocrine resistance, with a higher proportion of *GATA3* mutations, hypermethylation of *ESR1* and increased activation of EGFR, though no specific data for dnMBC is available.[7] In the analysis of the large SEER database including ~19,400 women with dnMBC, young age (<40 years) was associated with improved outcomes particularly when compared with elderly patients (mOS 43 *versus* 18 months).[25]

A few studies have reported evidence on dnMBC in young women separately. A comparison of clinical features and outcomes of women aged ≤40 years *versus* older women aged 41–69 years within a large real-world study (ESME) collected data on 4524 dnMBC tumours, with 598 (13%) from women aged ≤40 years.[36] Younger patients had a lower proportion of HR+/HER2- tumours (48.3% *versus* 60.9% in older patients, respectively), opposite to what observed for HER2+ tumours (34.6% *versus* 26.4%) and TN tumours (17.1% *versus* 12.7%). Younger women also had more undifferentiated and fewer lobular tumours.[36] No difference between visceral *versus* non-visceral metastases was observed but younger women had significantly more liver involvement (38.1% *versus* 30.7%), whereas older women had involvement of ≥3 metastatic sites (16.5% *versus* 22.4%).[36] Remarkably, younger patients with dnMBC had an overall 10-month improvement in mOS (59.9 *versus* 49.1 months), which was appreciable in the HR+/HER2- subtype (58.5 *versus* 52.3 months) but not in TN tumours. In multivariate analysis, dnMBC was confirmed as an independent prognostic factor in the former subtype.[36]

Similar findings were reported in an analysis of the SEER database on patients aged <60 years with stage IV breast cancer diagnosed from 2010 to 2014, which identified 6302 patients, 944 (15%) of whom were aged <40 years.[21] In this analysis, again younger women were more likely to have HER2+ tumours (36% *versus* 27%) and less likely to have HR+/HER2- tumours (44% *versus* 50%; $p<0.0001$) as compared with the older counterpart.[21] Amongst patients with HR+/HER2- tumours, younger women were more likely to have high-grade tumours and bone and liver metastases as compared with the older cohort. Survival was increased in women <40 years overall (mOS 45 *versus* 33 months, respectively; $p<0.001$) and across all subtypes except for TN tumours.[21] In the HR+/HER2- group, mOS was improved by 6 months (45 *versus* 39 months; $p=0.001$) in younger women despite more unfavourable features.[21]

The prospective observational study Prospective Outcomes in Sporadic *versus* Hereditary breast cancer (POSH) enrolled ~3000 women aged 40 years and younger diagnosed with breast cancer in the United Kingdom from 2000 to 2008. Only 2.6% (76) of women had dnMBC and 27.1% (786) developed rMBC at the time of analysis (2016) and were categorized according to MFI <12 months, <24 months, 24–60 months and >60 months. Patients with dnMBC had larger and more undifferentiated tumours only as compared with tumours in those with late rMBC but not with tumours recurring within 24 months. ER+ tumours were more common in the dnMBC group as compared with rMBC after 24 months, whilst HER2+ tumours were more frequent in the de novo cohort as compared with rMBC, independently of MFI. Bone remained the most common site of metastases in all groups. Women with dnMBC were more likely to have multiple metastatic sites (about 26%) and had the highest brain involvement (nearly 40% attributable to the high prevalence of HER2+ tumours). On the contrary, visceral metastases were more common in rMBC. Patients with dnMBC had a reduced risk of death as compared with all cohorts of rMBC, which was not significant but still nearly two-fold lower when compared with the late recurring subgroup and had also a significantly improved post-distant recurrence survival as compared with all rMBC cohorts. The study also reported extensive data on

BRCA mutational status, which was available for the entire study population. Interestingly, in the dnMBC cohort, a higher than expected prevalence of *BRCA2* mutation carriers was detected (11.8% *versus* 5% in all the remaining study population), whilst the opposite was observed for *BRCA1* mutations, which were detected in 9% of patients recurring <12 months and in only 1.3% of those with dnMBC.[48]

Overall, these findings suggest that, differently to what is observed in the early setting, age does not represent an adverse prognostic factor in young women with dnMBC, who show a better outcome either when compared with the older counterpart and with recurrent tumours.

Male breast cancer

Male breast cancer accounts for about 1% of all breast cancers. Given this low incidence, studies dedicated to male breast cancer are rare but the incidence of dnMBC in males in large databases from the USA, the National Danish registry and the EORTC male breast cancer programme ranged from 4% to 9%, similar to what is observed in women.[49–52] Differently from what is observed in female dnMBC, the proportion of HR+/HER2- dnMBC was higher in the TN and HER2+ subgroups as compared to the HR+/HER2- cohort in men (33% *versus* 15% *versus* 7.6%, respectively).[50]

Again, the greatest source of data on dnMBC in men derives from the SEER database. Data from 250 men diagnosed with de novo stage IV breast cancer between 2010 and 2017 were extracted from SEER.[53] Median age was 64 years; as expected, HR+/HER2- was the most common subtype (57.2%), followed by HR+/HER2+ (17.2%), TN breast cancer (7.6%) and HR-/HER2+ (1.2%).[53] When compared with the other stages in the same male population, dnMBC represented ~9% of all breast cancers and, unexpectedly, the proportion of dnMBC was relatively higher in TN (33.9%) *versus* 25.3% in HER2+ and only 7.6% in HR+/HER2- tumours.[53]

Overall, more than half of patients had a single metastatic site, mostly in bone. In patients with HR+/HER2- tumours, bone was the most common metastatic site, being present in 57% of patients, followed by lung (37%), liver (11.2%) and brain (4.2%).[50]

Patients with HR+/HER2- disease had a mOS of 33 months (95% CI 28–54 months), comparable with that of patients with HR+/HER2+ (35 months), whereas patients with TN breast cancer had the shortest survival (mOS 9 months). Patients with bone-only metastases had a statistically significant longer survival than patients with visceral metastasis (mOS 33 *versus* 20 months) irrespective of tumour subtype. No association between number of metastatic sites and outcome was observed.[53]

In a study comparing outcomes in male breast cancer with the female counterpart in a SEER database, male patients with HR+/HER2- MBC had generally a slightly inferior OS but not in the dnMBC cohort.[46]

Systemic treatments

Evidence from randomized clinical trials

As discussed above, a plausible explanation for the improved prognosis of dnMBC as compared to that of rMBC is the better response to systemic treatments. This hypothesis is based on a supposed reduced risk of acquired resistance in treatment-naive patients but whether it is supported by evidence remains unclear. Until recently, data for patients with dnMBC have not been reported separately either in randomized trials or retrospective analyses.

Partly comparable to a dnMBC population are patients enrolled in the FIRST and the FALCON studies comparing the SERD fulvestrant with the non-steroidal aromatase inhibitor (NSAI) anastrozole in the first line.[54,55] The FIRST study included a high proportion (75%) of treatment-naive patients despite not specifying whether they were diagnosed with stage IV breast cancer or whether they had not undergone adjuvant endocrine therapy for whatever reason.[54] Only treatment-naive patients significantly benefitted from fulvestrant (HR 0.63, 95% CI 0.42–0.93).[54] In the FALCON study, only 1% of patients had received endocrine therapy and ~30% had received chemotherapy in all settings; additionally, the benefit of fulvestrant was significant only in untreated patients (HR 0.752, 95% CI 0.59–0.97).[55]

More recently, pivotal studies investigating the combination of CDK4/6 inhibitors (CDK4/6i) and endocrine therapy included relevant proportions of up to 40% of dnMBC,[56–71] though this represented a stratification factor only for the PALOMA-2 and MonaLEEsa-3 trials.[56,57]

Interestingly, the proportion of dnMBC increased with age in the PALOMA-2 and MONARCH-3 trials, with >50% of women being older 65 years.[58,59]

Results of OS in the de novo and recurrent cohorts reported in clinical trials are summarized in Table 2.

Only the MonaLEEsa-2 trial reported outcomes of the de novo cohort separately.[60] The proportion of patients with de novo disease was the same in both treatment arms (34%); at the time of the first-line progression-free

Table 2. Outcomes in de novo MBC and recurrent MBC subgroups in studies with CDK4/6 inhibitors and endocrine therapy.

Author (year)	Study design	Treatment	dnMBC (%)	PFS dnMBC (months)	HR 95% CI	OS dnMBC (months)	HR 95% CI	PFS rMBC (months)	HR 95% CI	OS rMBC (months)	HR 95% CI
O'Shaughnessy (2018)[60] Hortobagyi (2022)[62]	Phase III R	Letrozole + Ribociclib/ placebo	34	NR *vs* 16.4	**0.45, 0.27–0.75**	NR *vs* 52.8	**0.52, 0.36–0.74**	ND	–	52.4 *vs* 51.2	0.91 (0.72–1.15)
Slamon (2021)[63]	Phase III R	Fulv + Ribociclib/ placebo	27.5	ND	–	59.9 *vs* 50.0	**0.62, 0.41–0.95**[a]	ND	–	–	–
Lu (2022)[64]	Phase III R	TAM o NSAI + Ribociclb/ placebo	41.6	ND	–	NR *vs* 49.6	**0.53, 0.36–0.79**	ND	–	48.6 *vs* 43.1	0.94, 0.71–1.24
Rugo (2019)[56]	Phase III R	Letrozole + Palbociclib/ placebo	37.2	27.9 *vs* 22	**0.61, 0.44–0.85**	ND	-	38.5 *vs* 16.6[b]	**0.52, 0.36–0.75**	ND	–
Llombart-Cussac (2021)[67]	Phase II R	Palbociclib + Fulv/LET	40.7	27.7 *vs* 32.9	1.14, 0.82–1.56	ND	–	28.1 *vs* 31.6	1.13, 0.77–1.75	ND	–
Albanell (2022)[68]	Phase II R	Fulv + Palbociclib/ placebo	45	33.4 *vs* 16.4	**0.29, 0.2–0.43**	ND	–	30.3 *vs* 27.3	0.77, 0.53–1.1	NR	–
De Michele (2021)[72]	R-W	Palbociclib + LET *vs* LET	40	ND	**0.57, 0.46–0.7**	ND	**0.56, 0.4–0.78**	ND	**0.58,[c] 0.47–0.72**	ND	0.78,[c] 0.58–1.06
Law (2022)[77]	R-W	Palbociclib + AI or Fulv	55	38.8	–	ND	–	30.5	–	ND	–
Wong (2022)[79]	R-W	Ribociclib + ET	26	NR	0.52, 0.27–1	ND	–	ND	0.59,[d] 0.32–1.07	ND	–

In bold statistically significant hazard ratio (HR).
[a]Endocrine therapy-naive population.
[b]rMBC with DFI >2 years.
[c]rMBC with DFI > 5years.
[d]rMBC with DFI > 1 year.
AI, aromatase inhibitor; DFI, disease-free interval; dnMBC, de novo metastatic breast cancer; ET, endocrine therapy; Fulv, Fulvestrant; LET, endocrine therapy with letrozole; ND, not determined; NR, not reached; NSAI, non-steroidal aromatase inhibitor; R, randomized; rMBC, recurrent metastatic breast cancer; R-W, real-world.

survival (PFS) analysis, median PFS (mPFS) was not reached *versus* 16.4 months in the CDK4/6i and placebo arms, respectively, with an approximate 55% reduction of risk of progression.[60] Final analysis of OS was recently reported showing a 12-month improvement for the ribociclib arm overall. (63.9 *versus* 51.4 months) whilst in the de novo disease cohort mOS was not reached *versus* 52.4 months in CDK4/6i and placebo arm respectively.[61] Interestingly, the HR was significant only in the de novo cohort (HR 0.52; 95% CI 0.36–0.74).[62]

The MonaLEEsa-3 study included 139 (27.5%) patients with dnMBC randomized in a 2:1 ratio to ribociclib or placebo.[57] Results for this cohort were not reported separately; however, in the endocrine-sensitive subgroup, which included either patients with de novo disease or relapsed after 12 months following completion of endocrine therapy, mPFS was not reached in the ribociclib arm and was 18.3 months in the placebo arm.[57] In the final OS analysis, patients in the endocrine therapy-naive subgroup, which included mostly patients with dnMBC, mOS was 59.9 *versus* 50.9 in the ribociclib and placebo arms (HR 0.62, 95% CI 0.41–0.95), and were higher as compared *versus* those reported in endocrine-sensitive patients (49.0 *versus* 41.8 months in CDK4/6i and placebo arms, respectively).[63]

The final survival analysis of the MonaLEEsa-7 study, which randomized 672 patients in premenopause and perimenopause with MBC to receive ribociclib or placebo plus NSAI or tamoxifen (+GnRH analogue), 40% of whom had dnMBC, showed a significant benefit with ribociclib in this cohort (mOS not reached *versus* 48.6 months in patients with rMBC) and a 6.5-month benefit in the placebo subgroups.[64]

Different results were obtained from the subgroup analysis of the PALOMA-2 study, in which 37% of patients included had dnMBC and were randomized in a 2:1 ratio to receive palbociclib or placebo both in combination with letrozole.[58] Extended follow-up analysis (38 months) showed a mPFS of 27.9 (22–34) months *versus* 22 (13–27.4) months with a HR of 0.61 (95% CI 0.44–0.85), which was lower as compared to subgroups of patients with a DFI of >2 years (38.5 months) or with other favourable prognostic factors as bone-only disease (36 months).[64] On the other hand, a higher ORR was observed in the de novo cohort as compared to relapsed patients irrespective of the treatment arm.[65] Detailed survival data for de novo disease are still not available, but an improvement in OS for palbociclib treatment was observed in the overall population (53.9 *versus* 51.2; HR 0.96, 95% CI 0.78–1.18; not significant).[66]

The phase II PARSIFAL trial randomized 486 untreated patients with MBC, including 40.7% with dnMBC, to palbociclib and placebo in combination with fulvestrant.[67] No difference in mPFS amongst the treatment arms was observed in patients with dnMBC as compared with patients with rMBC (28.1 months *versus* 31.6 for the fulvestrant and letrozole arm in the former and 27.7 months and 32.9 months in the fulvestrant and letrozole arms in the latter cohort, respectively). Similarly, no difference in the preliminary OS analysis was observed.[67]

Another small phase II study (FLIPPER) randomized 189 patients, 45% of whom had dnMBC, to fulvestrant with palbociclib/placebo.[68] The benefit of palbociclib was significant only in the dnMBC subgroup but a large difference in mPFS between the placebo arms (27.3 and 16.4 months in rMBC and dnMBC, respectively) rather than a greater efficacy of palbociclib in the dnMBC subgroup may be responsible of this finding.[68]

The MONARCH-3 study evaluating the combination of abemaciclib or placebo and a NSAI as first-line treatment in a 2:1 ratio included 196 (39.8%) patients with dnMBC. De novo disease was not a stratification factor, so no detailed data in this subgroup was available, but a significant PFS benefit similar to what observed in the rMBC subgroup was demonstrated (HR 0.47, 95% CI 0.31–0.72).[69] In addition, dnMBC was not an independent prognostic factor.[69,70]

An FDA pooled analysis of the 7 pivotal trials (MONARCH-2, MONARCH-3, MonaLEEsa-2, MonaLEEsa-3, MonaLEEsa-7, PALOMA-2, and PALOMA-3) reported a prevalence of 29% for dnMBC tumours.[71] Overall, a 3.5-month increase in PFS was observed in patients with dnMBC (mPFS 11.6 *versus* 8.1 in rMBC) but, in patients treated with NSAI plus CDK4/6i (~34%), the overall median improvement in PFS was 13.2 months superimposable to the 13.1 month benefit in patients with rMBC, though mPFS was not estimable in two trials for the de novo cohort.[71]

Evidence from real-world studies

An increasing amount of data is arising from real-world studies with CDK4/6i. Additionally, in routine practice, the proportion of patients with dnMBC is much higher than that reported in epidemiological reports, with the number reaching up to 40% of the population observed.[72–79]

One of the largest real-world studies derives data from the Flatiron's health longitudinal database, which includes de-identified electronic health records from more than 280 cancer clinics and represents 2.4 million patients with cancer treated in the USA.[72] This retrospective observational study included 1430 patients receiving first-line treatment with palbociclib and letrozole or letrozole alone for MBC from 2015 to 2019. Statistical methodologies were applied to overcome the potential biases

of a non-randomized comparison. Patients with dnMBC represented ~40% of the study population. Palbociclib treatment induced a similar PFS improvement in dnMBC and rMBC (HR ~0.60 for all groups independent from DFI), whilst the OS benefit appeared significant in the dnMBC cohort, differently from the rMBC cohort except for the very small subgroup of patients recurring within 1 year who unexpectedly performed with endocrine therapy alone much better than expected, but the very small size of this group (25 and 22 patients in the combination and endocrine therapy arms, respectively) affects the reliability of this observation.[72] PFS results were comparable to those observed in the PALOMA-2 trial, supporting the strength of this real-world evidence.[72]

A larger study using the same database and including 2,880 patients treated for their MBC with palbociclib and a NSAI from 2015 to 2020 has been recently published (P-REALITY X).[73] A significant OS benefit for the palbociclib combinations *versus* the NSAI arm consistent with both statistical methods used (49.1 *versus* 43.2 months, HR 0.76, 96% CI 0.65–0.87; $p<0.000$, with the stabilized inverse probability treatment weighting analysis, and 57.8 months *versus* 43.5 months, HR 0.72, 95% CI 0.62–0.83; $p<0.0001$, with propensity score matching analysis) was confirmed.[74] As for dnMBC, the significant benefit of the addition of palbociclib was confirmed and was similar to that of patients with disease recurring after >5 years.[73]

The Ibrance Real world Insights Study (IRIS) is a worldwide retrospective study based on medical chart review of patients who received palbociclib in combination with an aromatase inhibitor (AI) or with fulvestrant.[74–76] The European cohort included 1723 patients, with 761 (44% of the total population) having dnMBC 88% of whom were treated with an AI and 12% with fulvestrant.[74] Similar data were obtained from the US cohort, which included 652 patients, with 44% having dnMBC tumours and 65% in the palbociclib plus AI and 17.8% in the palbociclib plus fulvestrant arm, respectively.[75] Separate analyses for patients with dnMBC were not reported, but the overall results were superimposable to those of the phase III studies.[74,75] An even higher proportion of dnMBC tumours were included in the smaller cohort from Canada (64% of the total 247 patients and 71% amongst patients treated with palbociclib and AI) had dnMBC.[76]

A smaller retrospective study retrieving data from another longitudinal US database (Syapse) analyzed the real-world effectiveness of single-arm palbociclib and an AI in 242 patients treated from 2015 to 2019, 55% of whom had dnMBC. In this subgroup, mPFS was 38.8 months *versus* 30.5 in patients with rMBC.[77]

A single US institution retrospective study including 222 patients with MBC treated with palbociclib and endocrine therapy (mostly AI) from 2015 to 2021 and including 29.7% with dnMBC, showed that this subgroup experienced an improved PFS as compared to those with recurrent disease.[78]

In the analysis of the North Carolina University database, an improved PFS of nearly 14 months (25.5 *versus* 11.9) was observed in patients with dnMBC treated with any first-line therapy, which reached a 19-month difference in the small number of patients treated with CDK4/6i.[39]

Very few real-world studies with other CDK4/6i separately reporting data for dnMBC are available.

A medicine access programme in Australia with the combination of first-line ribociclib and endocrine therapy included 140 patients with 26% having dnMBC. Overall mPFS was not reached; in patients with dnMBC, mPFS was not reached and multivariate analysis showed a trend towards a longer PFS (HR 0.47; $p=0.06$) when compared with patients with early rMBC (<12 months) and/or recurring during adjuvant therapy.[79]

In summary, results of both clinical trials and real-world studies appear to confirm that patients with dnMBC respond better to systemic treatments; whether this improved benefit derives from a lower likelihood of acquired resistance or to intrinsic genetic and biological peculiarities, for example, reduced heterogeneity, needs still to be clarified.

Locoregional treatments

Consensus on the locoregional treatment (LRT) of dnMBC is highly controversial, and the management of these patients remains a therapeutic challenge. Systemic therapy is considered the main approach for these patients. Previous evidence has shown no survival benefit for patients with dnMBC treated with surgery for the primary tumour; therefore, LRT has generally been used only as palliative treatment to alleviate symptoms. However, in recent years, the scenario has rapidly changed as recent studies have shown how surgery with or without radiotherapy may be a potential means not only to control locoregional disease but also to improve survival in patients with dnMBC.

Several theories attempt to explain the possible benefit of LRT in dnMBC. First, the rationale for tumour debulking is to reduce the global tumour burden, thus increasing the efficacy of systemic therapy; second, removal of the primary tumour could reduce tumour-related immunosuppression and stimulate the immune response of the host and could reduce the source of cancer stem

cells, which have been associated with the emergence of resistance to therapy and which may lead to more aggressive disease.[80]

In contrast, some argue that the primary tumour may be a source of antiangiogenic factors and growth factor inhibitors; therefore, its removal may lead to a more rapid relapse. Finally, other potential drawbacks may be related to the release of growth factors associated with the surgical wound and to immunosuppression induced by the surgery itself.[80]

Evidence from retrospective studies

Recent large, real-world databases from Europe and the USA (reviewed in ref.[81]) have shown that ~40% of women undergo LRT in the context of dnMBC. Numerous meta-analyses have attempted to summarize data in the attempt to overcome several biases deriving from the relevant heterogeneity but drawbacks in the studies included affect the conclusions.[81]

The majority of the retrospective studies examined did not include information on tumour subtypes, therefore limiting the application of findings in current clinical practice.[81] Other important biases are timing bias, for example, different timing of patient inclusion at diagnosis of dnMBC or after a systemic therapy, which could have selected for patients with a better prognosis; patient selection bias, for example, the trend to propose LRT to younger and healthier patients and with oligometastatic disease; and treatment-related biases, for example, the lack of information on response to systemic therapy, the long recruitment period, which encompasses different available therapies, and the heterogeneity of treatments (systemic or LRT).[81]

One of the most recent and largest meta-analyses assessing the role of LRT in dnMBC included 42 studies retrospective and 5 prospective studies with more than 210,000 patients.[82] The results showed that all types of LRT significantly reduced mortality by 31.8% (n=42; HR 0.68, 95% CI 0.64–0.73); in particular, surgical resection of the primary tumour appeared to reduce mortality by 36.2% (n=37; HR 0.6379, 95% CI 0.60–0.68). The results show that LRT of the primary tumour appears to improve OS in dnMBC and strengthens the use of LRT in metastatic disease.[82]

Most retrospective studies have evaluated the prognostic role of LRT, particularly surgery of the primary tumour according to the metastatic pattern, highlighting a definite benefit in patients with bone-only disease.[81,83] Only recent studies have included tumour subtype amongst the prognostic factors.

Evidence from prospective randomized trials

Results of prospective randomized trials are quite inconsistent as are their design and inclusion criteria. The monocentric Indian study included only patients previously submitted to systemic therapy that was not assigned according to tumour subtype and, moreover, it was not continued after local treatment. LRT improved only local control but not OS.[84]

A small, single-arm, prospective trial (TBCRC 013) included 112 patients (63% HR+/HER2−) with dnMBC undergoing upfront systemic therapy; 85% of patients were classified as responders (including those with stable disease) and were offered surgery, but this did not improve 3-year OS in the 41% of patients choosing this option, irrespective of tumour subtype.[85]

In a Turkish study (MF07.01), 274 patients were randomized to upfront systemic therapy or to surgery with or without radiotherapy of the primary tumour followed by systemic therapy.[86] Tumours were not classified by tumour subtype but as HR+ or HR− and HER2+ and HER2−; HR+ tumours were statistically more frequent in the surgery group (86% *versus* 73%), whilst all the other variables, including treatment choices, were well balanced between the two groups. An unplanned analysis showed a statistically significant benefit for the surgery arm only in patients younger than 55 years, with HR+/HER2− tumours and with solitary bone-only disease. As expected, local progression rate was significantly lower in the surgery arm (1% *versus* 11%).[86] At a 10-year follow-up, OS was still significantly improved by LRT: patients with HR+ tumours had a mOS of 48 months after surgery *versus* 42 months and, differently from the previous analysis, OS was improved irrespective of HER2 status.[87] Importantly, with an extended follow-up, overall OS was also improved after LRT (mOS 46 *versus* 35 months), leading to a 29% lower risk of death. Patients with visceral metastases did not derive any benefit from treatment of the primary tumour.[87] However, the generalization of the results of this study has been questioned because of the imbalance of favourable prognostic factors (HR+ tumours, bone-only disease) between arms and in comparison with other trials.[80]

A subsequent study from the same group prospectively investigated the sequence between systemic therapy and surgery in patients with bone-only dnMBC.[88] This prospective registry study included 505 patients who received upfront systemic therapy (240 patients) or surgery (265 patients); patients in the latter group could receive local treatment before or after systemic therapy. The two groups were balanced for tumour biology but not for the extension of primary tumour and

of metastatic sites since, in the systemic therapy group, a significantly greater proportion of patients had multiple bone metastases, whilst patients in the upfront LRT group were younger and had a higher rate of T3 tumours. Overall, surgery either upfront or after systemic therapy improved OS. In patients with HR+/HER2- tumours, which represented ~63% of patients, mOS after combined treatment was not reached *versus* 55 months in the surgery and systemic therapy group, respectively (HR 0.45, 95% CI 0.31–0.67; $p<0.0001$). As expected, locoregional disease control rate was greater in the LRT arm, with a progression rate of 6.7% *versus* 16.2% in the systemic therapy arm. In this study, the benefit of LRT was observed also in HER2+ but not in TN tumours and was independent of the extent of bone disease and of the sequence between systemic therapy and LRT.[88]

Two other randomized studies, the Austrian POSYTIVE trial and the US E2108, both including patients who had received upfront systemic therapy, failed to show any advantage in OS for LRT.[89,90] The Austrian study closed prematurely due to slow accrual, including only 90 of the 254 planned patients.[89] The study randomized patients to upfront surgery *versus* initial systemic therapy and showed a mOS of 34.6 *versus* 54.8 months in the two groups (HR 0.69, 96% CI 0.36–1.33). Patients with luminal A tumours (46/90 patients) did worse after early surgery (HR 0.276, 95% CI 0.10–0.18), whilst a trend toward benefit was observed amongst the very few patients ($n=12$) with luminal B tumours; however, the very small number of patients in this group does not allow any conclusion to be drawn.[90] Surgery showed only a trend towards a lower locoregional progression rate. A 20% rate of tumours with involved margins after surgery may have contributed to the latter finding. Patient-reported quality of life outcomes did not differ amongst treatment groups. Due to the limited numbers, the results of this study should be considered with caution.[89]

The US E2108 study randomized 256 patients who had not progressed after a maximum of 32 weeks of systemic therapy to surgery or continuation of therapy.[90] This study also did not reach the full planned accrual. Overall, no difference in mOS was observed (53.1 *versus* 54.9 months in the systemic and surgery groups, respectively). Nearly 60% of randomized patients had HR+/HER2- tumours, and no difference in OS was observed in this subgroup between surgery and no surgery (HR 0.88, 95% CI 0.56–1.39).[90] On the other hand, the locoregional progression rate was significantly lower in the surgery arm (16.3 *versus* 39.8% at 3 years). Patient-reported quality of life outcomes were similar amongst groups.[90]

A meta-analysis of the four randomized trials found no benefit for LRT either overall or for patient-specific subgroups defined according to HR and HER2 status or metastatic disease extent (bone *versus* visceral).[91] Only time to local progression was significantly improved by LRT, which negatively affected time to distant progression.[91]

Another meta-analysis including a total of 1110 patients from six prospective trials showed that, compared with no surgery, surgery did not prolong OS but had a significantly longer locoregional PFS (HR 0.23; $p<0.001$).[92] Only patients with a single bone metastasis derived a survival advantage (HR 0.47; $p=0.04$).[92]

Evidence from real-world studies

In addition to randomized trials, large-real world series have been recently reported, confirming a benefit for LRT.[93,94] The analysis of two large databases from China including patients diagnosed from 2004 to 2018, retrieved 987 patients with dnMBC, 47% of whom underwent surgery of the primary tumour.[93] As expected, the two groups were not balanced for patient and disease characteristics, with a prevalence of low burden and bone-only disease amongst the surgery group. In addition, surgery could be performed upfront or after induction systemic therapy. Surgery significantly improved OS overall (mOS survival 45 *versus* 28 months) and in all subgroups except in patients with brain metastasis and TN tumours; interestingly, delayed surgery after systemic therapy significantly prolonged OS as compared to upfront surgery (mOS 94 *versus* 40 months), though no information on sensitivity to systemic therapy was reported.[93]

The ESME database was used to compare outcomes of patients with dnMBC treated with systemic therapy alone or in combination with LRT, which included either surgery alone or surgery plus radiation therapy. Overall, combination therapy conferred a survival advantage, which was confirmed also in patients with HR+/HER2- tumours (mOS 61.6 *versus* 45.9 months) and in patients with HER2+ but not with TN tumours. However, again, the two groups were imbalanced since younger patients and those with bone-only and/or a single metastatic site were significantly more represented in the combination arm.[94]

Unresolved issues are also the type of surgery, the role of radiotherapy, and local treatment of metastatic sites. Despite no controlled trial having investigated this issue, generally, tumour resection (provided clear margins are obtained) is considered adequate surgery, whilst the treatment of axillary nodes is debatable given the increased risk of morbidity associated with dissection.[81]

The role of radiotherapy either as an alternative or in addition to surgery is highly controversial. Several non-ran-

domized retrospective studies have revealed that radiation therapy might confer a survival benefit.[81]

A retrospective analysis of the National Cancer Database identified 12,838 women with stage IV breast cancer diagnosed from 2010 to 2015 and showed that the addition of surgery and radiation therapy to systemic therapy significantly improved OS in patients with HR+ and HER2+ breast cancer, the latter group experiencing the largest benefit.[95] As for other retrospective series, this had selection biases as a larger proportion of patients with good prognostic factors (young age, bone and single metastatic site) receiving multimodality treatment were present.[95]

The same database was analyzed to investigate the impact of multimodality LRT in male dnMBC. The study included 539 men diagnosed with dnMBC from 2004 to 2017 with known HR but unknown HER2 status and showed that, in patients with ER+ MBC, accounting for more than 90% of cases, the combination of systemic therapy, surgery and radiation therapy conferred a 5-year survival advantage as compared to the combination of surgery and systemic therapy or systemic therapy alone (40%, 27% and 20%, respectively).[96] In women, no benefit for HR− tumours was observed.[96]

Despite no consensus existing on specific prognostic factors, selected patients, for example, those with better performance status, low tumour burden and HR+ tumours, should be considered for radiation therapy after surgery of the primary site.[97]

The role of radiotherapy as an alternative to surgery is highly controversial, and there are little data in the literature to support this possibility. This approach may have some advantages as a palliative option in selected patients, especially in elderly patients with the aim to spare surgery-associated complications and localized disease.[81]

As for local treatment of metastatic sites, some evidence suggests that, in oligometastatic disease, local treatment of all sites is associated with prolonged survival, especially in bone-only disease. Two prospective phase III trials (NCT02089100, NCT02364557) are currently under way to investigate the role of stereotactic body radiotherapy or surgery with curative intent in oligometastatic breast cancer, not exclusively dnMBC.[81]

Despite conflicting evidence arising from clinical trials, evidence emerging from recent retrospective studies reporting data according to several prognostic factors led to the development of the 5th ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC5) recommending a multimodality approach, including LRT with curative intent especially for those with bone-only disease, which accounts for ~30% of dnMBC.[81,98] Preferred candidates for LRT are patients with a low disease burden, especially if bone-only disease, with HR+ and HER2+ tumours, and who obtain disease control after induction systemic therapy.[81,98]

Conclusions

Evidence summarized above shows that HR+/HER2− dnMBC represents a peculiar entity. Patients with dnMBC have a better prognosis than women with rMBC, with mOS approaching 5 years in patients with favourable prognostic factors.

Paradigm of the clinical diversity between rMBC and dnMBC is the favourable prognosis observed in women aged 40 years and younger with dnMBC compared with these representing poor prognosis in patients with early MBC and rMBC.

The reduced likelihood of acquired resistance to adjuvant treatment may partially explain the improved outcomes but inherent genomic and biological peculiarities, presently not yet fully elucidated, can also contribute to the behaviour of dnMBC, as suggested by the better outcomes after first-line systemic treatment observed in the randomized trials and real-world series.

Despite the intrinsic limitations of the retrospective studies and the controversial results of the randomized studies not allowing consensus on the role of LRT, it is reasonable to consider LRT for patients with HR+/HER2− dnMBC, with bone-only disease, who have benefitted from systemic treatment and are unlikely to experience surgery-related morbidity. In case of low-burden visceral disease, a case-by-case multidisciplinary evaluation should be performed considering the feasibility of treatment of metastatic sites.

In the increasing complexity of the heterogeneous landscape of MBC, improved knowledge of the genomic, biological and clinical features of dnMBC may help to further tailor treatment strategies that account for the peculiarities of this subset of tumours. In the near future, the planned extensive analyses of tissue and biological samples collected from patients enrolled in recent first-line trials that have included substantial proportions (up to 40%) of patients with dnMBC will likely provide more reliable answers, allowing the optimization of treatment and improved prognosis of this peculiar tumour type. Altogether, genomic, biological and clinical findings indicate that HR+/HER2− dnMBC is a peculiar entity as compared with rMBC and deserves a dedicated treatment algorithm.

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