



Review

Male breast cancer: An update in diagnosis, treatment and molecular profiling

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ABSTRACT

Significant advances have been made in the diagnosis and treatment of female breast cancer, resulting in a decline in incidence and a global improvement in clinical outcome. The statistics for male breast cancer (MBC) stand in sharp contrast—over the past several decades, there has been a steady rise in the incidence of this disease, and clinical outcome has improved at a much slower pace. In the current review, the clinicopathologic features of MBC are described in detail. An emphasis is placed on molecular profiling of MBC, which may identify candidate biomarkers and putative targets for pharmacologic intervention. The current role of cytotoxic chemotherapy and endocrine therapy (including tamoxifen, aromatase inhibitors and GnRH analogues) is defined in the context of currently available studies. Furthermore, the potential role of targeted agents, including HER2-directed therapies, PARP inhibitors, and angiogenesis inhibitors, is delineated.

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1. Introduction

In recent years, much attention has been garnered by data suggesting a drop in the incidence of breast cancer [1]. This trend has been attributed to a decline in use of hormone replacement therapy amongst post-menopausal females according to data reported from the Women's Health Initiative [1,2]. In contrast, the incidence

of male breast cancer (MBC) appears to be rising. Review of Surveillance, Epidemiology and End Result (SEER) data indicate a rise in the incidence of MBC, from 1.0 per 100,000 men in the late 1970s to 1.2 per 100,000 men from 2000 to 2004 [3]. A similar analysis of the United Kingdom Association of Cancer Registries (UKACR) database identified a parallel trend, with the incidence of MBC rising steadily between 1985 and 2004 (Fig. 1) [4]. Furthermore, while it is widely cited that MBC accounts for less than 1% of all cases of breast malignancy, these figures are highly discrepant amongst series, possibly varying due to differences in geography and race [5–8]. For instance, separate single institution studies in India and

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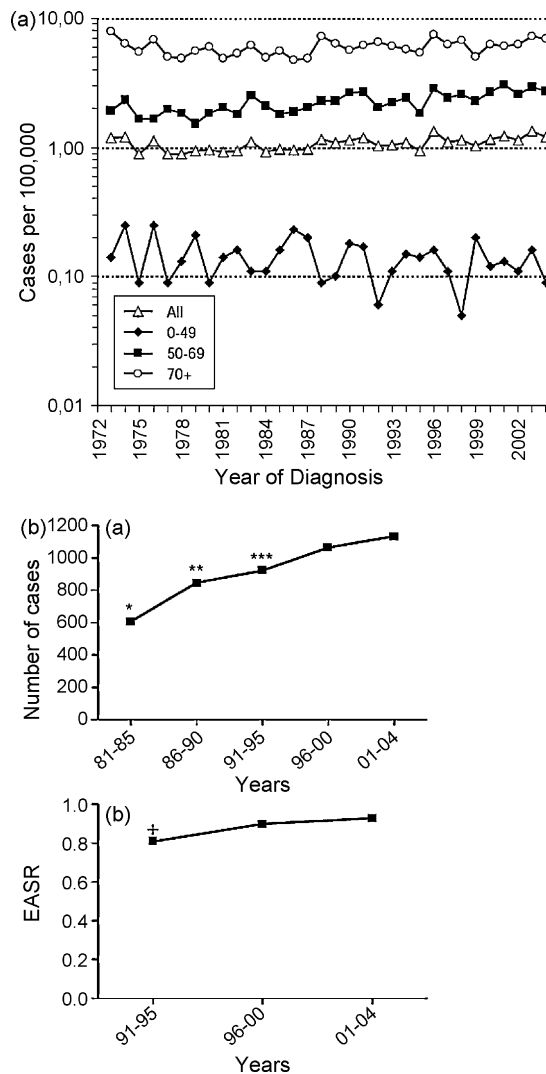


Fig. 1. A steady rise in the incidence of MBC has been documented in SEER registry analyses (a) and an evaluation of the UKACR (b). (Figures adapted from [3,4]).

Pakistan suggest that MBC represents up to 2.5% and 5.9% of breast cancer in both genders, respectively [9,10]. With respect to race, SEER data indicates that African American males have a significantly higher likelihood of developing breast cancer as compared to whites or Asian Americans/Pacific Islanders [11].

Thus, with the incidence of MBC on the rise and the prevalence potentially underestimated, there is a need to better understand the clinicopathologic features of this disease. Furthermore, it appears that males have derived lesser benefit from the substantial advances in breast cancer therapy made over the past several decades. A recent analysis of SEER data investigating trends in survival amongst patients diagnosed between 1996 and 2005 suggested a 42% decrease in breast cancer-related death amongst women, but only a 28% decrease amongst men [12]. In the current review, emerging data related to MBC diagnosis and treatment is presented. The role of molecular profiling is emphasized, given a burgeoning pipeline of targeted agents that have already changed the landscape of breast cancer therapy.

2. Risk factors

A number of studies have assessed risk factors for MBC. A total of 121 males who ultimately developed breast cancer were identified from the prospective National Institute of Health (NIH)-AARP

Diet and Health Study [13]. In this analysis, report of a first-degree relative with male breast cancer (relative risk, RR, 1.92; 95%CI 1.24–3.91) and elevated body mass index (>30 versus <25; RR 1.79, 95%CI 1.10–2.91) were associated with development of MBC, while physical activity was inversely related. A separate analysis of the US Veterans Affairs database identified 642 MBC patients [14]. In this analysis, risk factors identified included diabetes (RR 1.30, 95%CI 1.05–1.60), orchitis/epididymitis (RR 1.84, 95%CI 1.10–3.08), Klinefelter's syndrome (RR 29.64, 95%CI 12.26–71.68) and gynecomastia (RR 5.86, 95%CI 3.74–9.17). Interestingly, amongst African American MBC patients, cholelithiasis was a significant risk factor (RR 3.45, 95%CI 1.59–7.47). The strong association of Klinefelter's syndrome with MBC observed in the Veterans study is echoed by several other reports; for instance, a Swedish registry study suggested a 50-fold increase in the risk of MBC amongst patients with Klinefelter's syndrome [15]. Moreover, the rate of Klinefelter's syndrome in affected patients was suggested to be as high as 7.5% in this experience. Several other risk factors for MBC identified by other studies include previous breast pathology, previous testicular pathology and a history of liver disease [16].

Interestingly, MBC may serve as a risk factor for other malignant processes. A review of 69 patients with MBC identified 12 patients (17%) with concomitant diagnoses of prostate cancer [17]. A theoretical link between these diseases does exist—for example, aromatase inhibitors used to treat MBC may increase serum levels of testosterone, thereby driving growth and proliferation of prostate cancer clones [18]. Although further prospective testing is needed to validate this association, the practitioner may choose to weigh this data in the risk: benefit decision to initiate prostate cancer screening in patients with MBC. Outside of prostate cancer, there is some suggestion that MBC may be associated with leukemia and cancers of the small intestine, rectum, and pancreas [19–21]. Other links between MBC and distinct malignancies may result from the presence of a *BRCA*-deficiency; these are addressed elsewhere in this manuscript. Finally, the association between breast cancer and meningioma in females does not appear to exist in males [22].

3. Diagnosis

The majority of patients with MBC present with a painless, subareolar mass, often associated with nipple retraction, ulceration, bleeding or discharge [5]. In the absence of other findings, it has been suggested that the presence of nipple discharge may be an indicator of non-invasive disease—hence, early recognition of this symptom is critical [23]. Bilateral involvement is rare, and is estimated to constitute less than 2% of cases [24]. Axillary node metastases appear to be more common in males as opposed to females, and cases of occult breast cancer have been reported in the literature [25,26].

Techniques used for diagnosis of female breast cancer may be relevant to MBC. A series of 517 fine-needle aspirations (FNAs) of the breast performed in males with abnormal clinical findings yielded 70 cases of carcinoma (13.8%), 29 inconclusive cases (5.7%), and 295 negative cases (58%) [27]. With histopathology available in 97 cases, it was suggested that the sensitivity and specificity for FNA approached 100%. In a more recent series of 217 patients evaluated for a breast mass with FNA, pathologic analysis suggested carcinoma in 12 cases (5.5%), suspicious findings in 5 cases (2.3%) and no malignancy in 181 cases (83.4%) [28]. In 26 of these cases (12%), matching biopsies were available. Similar to the previous study, the sensitivity and specificity for detecting malignancy with FNA was 100% [28].

The technique of sentinel lymph node (SLN) biopsy has also been explored in MBC. Amongst 7,315 SLN procedures performed at the Memorial Sloan-Kettering Cancer Center (MSKCC) over a 10-year period, 78 (1%) were in males [25]. Clinical follow-up was available

Table 1
Receptor status of male breast cancer as defined in recent series.

Reference	N	ER+	PR+	HER2+
Avisar et al. [40]	18	94%	–	56%
Ferreira et al. [58]	30	87%	87%	–
Giordano et al. [38]	2537	55%	39%	–
Nahleh et al. [39]	612	60%	53%	–
Shah et al. [41]	32	80%	70%	30%
Stalsberg et al. [29]	282	87%	76%	–

in 76 of these patients. A negative SLN was detected in 39 patients (51%)—of these, a positive non-SLN was detected in 2 patients (8%) by intra-operative palpation. Amongst 37 patients with positive SLNs (49%), the majority had nodal positivity determined intra-operatively and proceeded immediately to axillary lymph-node dissection. With a median follow-up of 28 months, no axillary recurrences were observed, suggesting the utility of this procedure in male patients.

4. Pathologic features

Several studies have characterized the frequency of histologic subtypes in MBC. Using data extracted from ten US registries, a cohort of 282 cases was identified with associated tissue specimens [29]. Roughly 90% of these specimens demonstrated invasive disease, and all of the remaining non-invasive cases were of the ductal subtype (given lack of terminal lobules in the male breast, lobular histologies are exceedingly rare) [5]. Amongst invasive histologies, a larger proportion of ductal and papillary subtypes were recorded as compared to what would be expected in females. Case reports document co-existence of these subtypes, and there are additionally published anecdotes of papillary variants [30,31]. Within the past several years, multiple reports of intracystic papillary carcinoma have been published [32–37]. This non-invasive subtype comprises less than 0.5% of all female breast cancer, but may constitute a more frequent entity in the setting of MBC.

Several series have identified a higher frequency of estrogen receptor (ER) and progesterone receptor (PR) positivity in MBC as compared to female breast cancer, suggesting the role of endocrine therapy in this population [38,39]. These data are summarized in Table 1. In more limited series, it appears that overexpression of human epidermal growth factor receptor-2 (HER2), occurring in 25% of female breast cancer cases, may be higher amongst male cases (30–56%) [40–43]. HER2, a transmembrane receptor, is the target of multiple novel agents, including trastuzumab, lapatinib and trastuzumab-DM1 [44–46]. Strategies using both endocrine therapy and HER2-directed agents in combination are currently being explored in the setting of female breast cancer, and may ultimately be applicable in MBC, as well [47,48].

5. Molecular profiling

Molecular characterization of MBC offers insights into potential therapeutic strategies. Outside of the clinically relevant receptor subtypes, there are a number of other molecular markers that have been assessed in the setting of MBC. For instance, microRNAs (miRNAs) represent ~22 nucleotide noncoding RNAs that may actually serve to modulate mRNA function [49]. In one report, RNA was isolated from paraffin embedded tissue derived from 23 male and 10 female breast cancer patients. RNA was subsequently hybridized to miRNA microarray platforms including 326 human genes and 249 mouse genes [50]. The study identified differential miRNA expression in 17 genes, with 4 genes upregulated and 13 genes downregulated. Quantitative real time-polymerase chain reaction (RT-PCR) was used to confirm these results, and immunohistochemistry (IHC) was used to determine whether pro-

tein expression varied as a consequence of miRNA expression. One of the downregulated miRNAs (miR-10b) is known to suppress expression of *HOXD10*, involved in cell migration and extracellular matrix remodeling. IHC analyses, as expected, did show high levels of *HOXD10* expression in MBC specimens, suggesting the putative role of *HOXD10* in this disease process. A second observation in the microarray study was downregulation of miR-126, a suppressor of vascular endothelial growth factor (VEGF) expression. Consequently, IHC experiments demonstrated strong expression of VEGF in MBC specimens. VEGF is a driver of tumor-related angiogenesis; several agents that antagonize VEGF-mediated signaling are currently either under development or in use for female patients with metastatic breast cancer (i.e., sunitinib, sorafenib and bevacizumab) [51–53]. Among these agents, bevacizumab is supported by several randomized, phase III trials demonstrating an improvement in progression-free survival (PFS) when added to cytotoxic chemotherapy [52,54,55]. Given the data presented herein, exploration of VEGF-directed therapies in MBC may be warranted.

The role of the prolactin receptor in breast cancer pathogenesis is controversial; however, data from prospective efforts do demonstrate a modest association between prolactin level and breast cancer risk [56,57]. In one series, tissue from 30 patients with male gynecomastia and 30 patients with MBC were assessed [58]. Prolactin receptor expression was significantly higher in MBC patients as compared to patients with gynecomastia (60% versus 20%, $P=0.003$). In contrast, ER and PR expression (also assessed in this series) did not appear to differ widely between these cohorts. Compounds antagonizing the prolactin receptor have been shown to augment the activity of doxorubicin and paclitaxel in cellular models; this approach may prove clinically useful in the setting of MBC [59].

A step lacking in most biomarker studies of MBC is correlation with clinical outcome. In a series of 39 patients with MBC and available tissue, survivin and COX-2 expression were determined [60]. Survivin is a member of the inhibitor of apoptosis (IAP) family of proteins, and overexpression of survivin may represent a mechanism of resistance to HER2-directed therapies [61]. COX-2 is a mechanistically distinct moiety, and metabolites of COX-2 (such as prostaglandin E₂, PGE₂) are thought to enhance tumor angiogenesis and suppress anti-tumor immunity [62]. Expression of both survivin and COX-2 were seen in a substantial number of patients (69% and 36%, respectively). Neither biomarker served to predict overall survival (OS), albeit in a relatively small sample. Despite the negative result, study designs such as this are useful in identifying the link between relevant biomarkers and prognosis.

While biomarker discovery in MBC is often driven by observations in female breast cancer, other strategies do exist. Matrix assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry is a novel method of determining differential protein expression in cancer tissue, and may ultimately define unique candidate biomarkers [63]. In a series of patients with MBC, tropomyosin-1 (a tumor suppressor) was shown to be underexpressed. Alterations in cathepsin D and galectin-1, mediators of cellular invasion and metastasis, were also observed. Outside of MALDI-TOF, methods such as comparative genomic hybridization (CGH) may identify broader genetic alterations that occur in MBC [64]. In a series of 39 MBC specimens assessed by CGH, gains were most frequently observed at 1q, 8q and 16p, and losses were most frequently observed at 8p, 16q, and 13q. More detailed exploration of these loci could yield moieties relevant to MBC pathogenesis.

6. BRCA-deficient MBC

Overall, it appears that *BRCA2* mutations occur more frequently than *BRCA1* mutations in MBC. A review of over 9000 breast cancer-

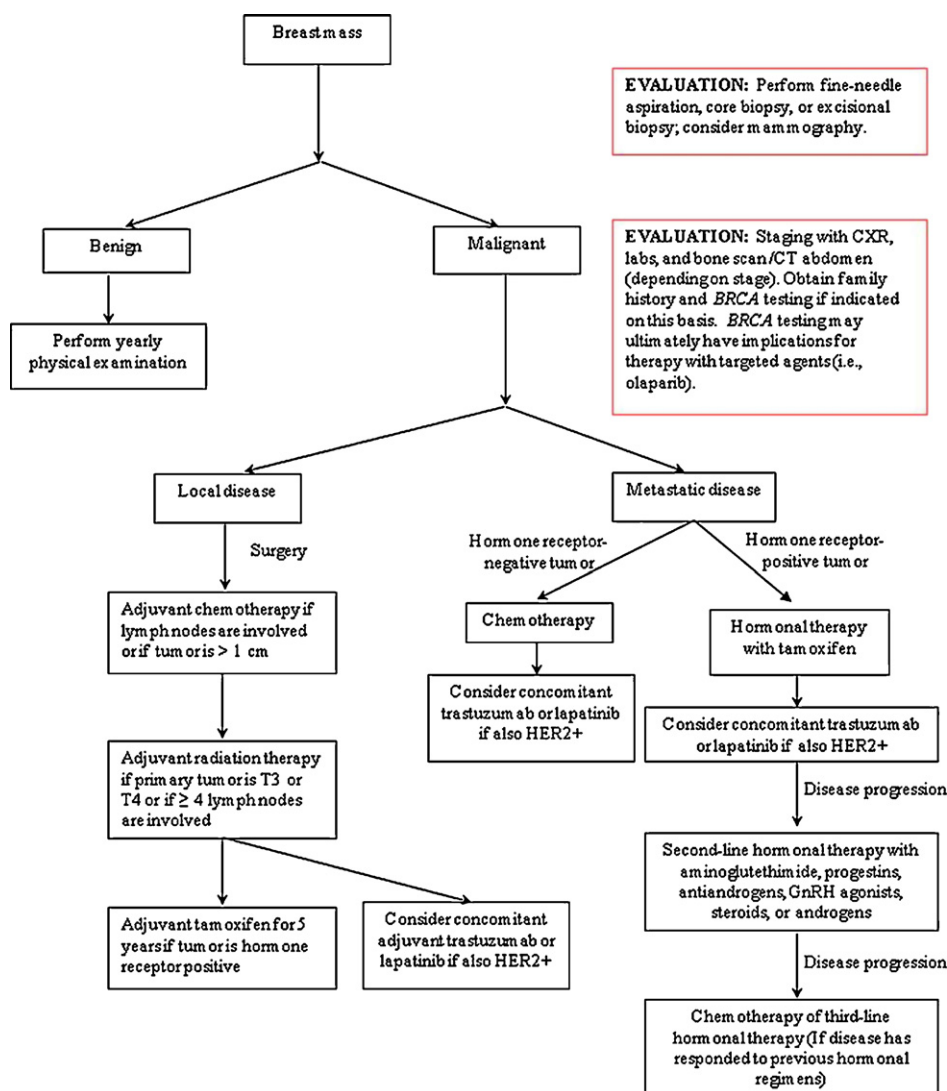


Fig. 2. A proposed schema for evaluation and management of MBC. (Adapted from [5]).

related referrals to the Regional Genetics service in Manchester, UK, identified 64 families with affected males [65]. Blood lymphocyte DNA testing from affected patients yielded 17 pathogenic *BRCA2* mutations and 4 pathogenic *BRCA1* mutations. Overall, the rate of *BRCA1/2* mutation in MBC families was 34%. This rate is substantially higher than in population-based studies; for example, another UK-based registry analysis identified 94 cases of MBC and identified mutations in only 15% of patients [66]. Similarly, a population-based series comprised of 54 MBC cases from Southern California identified *BRCA2* mutations in only 4% of patients. In this series, no *BRCA1* mutations were found, and only 13% of patients had a family history of breast and/or ovarian cancer.

A new class of agents has shown promising activity in breast cancer patients with DNA-repair defects. The enzyme poly(ADP-ribose) polymerase (PARP) complements *BRCA*-related repair processes; drugs targeting PARP may therefore be particularly active in *BRCA*-deficient patients (a concept termed 'synthetic lethality') [67]. The oral PARP inhibitor olaparib has been examined in a cohort of 54 patients with *BRCA1/2*-deficient, metastatic breast cancer who had been previously exposed to a median of 3 lines of chemotherapy [68]. In this heavily refractory population, an overall response rate (ORR) of 38% was observed in 27 assessable patients. Toxicities related to the agent were relatively mild, with fatigue, nausea and vomiting representing the most frequently reported

adverse events. Outside of targeted therapies, there is emerging evidence suggesting that DNA-damaging cytotoxic agents (such as cisplatin) may be particularly effective in *BRCA*-deficient breast cancer [69]. The association observed between MBC and *BRCA*-deficient disease suggests the potential applicability of olaparib, cisplatin and related agents in this disease process, although this clearly requires further clinical validation.

7. Treatment

7.1. Systemic therapy

The increased incidence of ER- and PR-positivity in MBC suggests the potential utility of endocrine therapy in this disease. As a result of the low incidence of MBC, there are no randomized trials to guide treatment [70]. Nonetheless, a prospective study of tamoxifen therapy for stage II and III operable MBC has been performed. Survival in this cohort of 39 patients was 61% at 5 years, which was significantly greater than the 44% 5-year survival observed in historical controls ($P=0.006$). Disease-free survival (DFS) at 5 years was also superior as compared to historical controls (56% versus 28%; $P=0.005$). With respect to toxicity data, no serious adverse events were recorded. On the basis of these data, it has been suggested that patients with operable MBC be treated with 5

years of adjuvant tamoxifen therapy if hormone-receptor positive (Fig. 2).

Akin to adjuvant endocrine therapy, use of adjuvant chemotherapy in MBC is guided by a relatively small dataset. In a prospective analysis, 24 patients with operable MBC were treated with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) after mastectomy [71]. At a median follow-up of 46 months, only 4 patients had recurred (2 had died of metastatic disease). In this study, 5-year survival was projected at greater than 80%. Importantly, all patients in this series had nodal involvement. Thus, for patients with high risk, operable MBC, consideration may be given to adjuvant chemotherapy. Limited data is available to guide whether more recently validated taxane- or anthracycline-based adjuvant regimens can be substituted for CMF.

In the setting of metastatic, hormone-receptor positive disease, orchiectomy was the first effective approach documented in the medical literature [72]. Modern endocrine therapies have also been effective; tamoxifen has demonstrated response rates of 49% in the setting of metastatic MBC [73]. Importantly, it appears that the benefit of endocrine therapy lies exclusively in the hormone-receptor positive population—in 43 patients with metastatic MBC treated with tamoxifen, a response rate of 69% was observed amongst 35 men with ER-positive disease, but no responses were observed amongst 8 men with ER-negative disease [73]. More recent data points to the utility of aromatase inhibitors in MBC, which have demonstrated superior activity to other endocrine therapies in metastatic female breast cancer [74]. Review of a French registry identified 15 patients treated with either exemestane, letrozole or anastrozole ($n=5$ for each) [75]. Two patients (13%) had a complete response to therapy, while 4 patients (27%) had a partial response. Stable disease was observed in a further 2 patients (13%), yielding an overall clinical benefit rate of 53%. Retrospective correlative studies in 6 assessable patients suggested that all had estradiol levels below the threshold of detection while on aromatase inhibitor therapy. Several subsequent reports have suggested that the activity of aromatase inhibitors can be augmented in MBC by combination with gonadotropin-releasing hormone (GnRH) analogues, such as leuprolide [76,77]. A lesser explored endocrine therapy in MBC is fulvestrant; this inhibitor of ER dimerization has been shown to have activity comparable to aromatase inhibitors in the setting of first-line therapy for metastatic female breast cancer, and demonstrates activity in the same group of patients after failure of tamoxifen [78,79]. Anecdotal reports suggest the efficacy of fulvestrant in metastatic MBC [80].

The role of chemotherapy in metastatic MBC is less clear. Retrospective studies directly comparing chemotherapy and endocrine therapy in this setting suggest greater efficacy from the latter, though it is recognized that chemotherapy may still have a palliative effect (for example, single agent cyclophosphamide offers response rates of up to 53%) [5]. The activity of novel cytotoxic agents has been documented only in small case series; for instance, one report suggested activity with the combination of gemcitabine and nab-paclitaxel in 2 patients with metastatic MBC [81]. The role of HER2-directed therapies is even more vague; though trastuzumab has now been in clinical use for nearly a decade, there are limited reports of its activity in MBC in the published literature [82].

7.2. Surgery and radiation

Despite a general adherence to female breast cancer guidelines, surgical management of MBC more frequently involves either radical or modified radical mastectomy [83]. In a review of 50 years of surgical experience at the Mayo Clinic, 124 patients with MBC were identified [84]. Of these patients, 92% were treated with mastectomy. Roughly equal proportions received radical and mod-

ified radical procedures (41% and 39%, respectively), while 12% received simple mastectomy alone. With two large studies in operable female breast cancer reporting the equivalence of mastectomy and breast-conserving approaches at 20-year follow-up, there has been keen interest in determining whether the latter approach is feasible in MBC [85,86]. In one series, 7 men with localized MBC were treated with breast conservation [87]. At a median follow-up of 67 months, no local recurrences were observed, suggesting the feasibility of this approach.

Despite conflicting datasets on the topic, current guidelines from the National Comprehensive Cancer Network advocate use of post-mastectomy radiation therapy (PMRT) in women with 4 or more axillary lymph nodes [88]. Further, strong consideration of the modality is recommended in the setting of 1–3 positive axillary nodes. For patients with MBC, limited data is available to support use of PMRT [5]. In a series of 42 MBC patients who received mastectomy, PMRT and either adjuvant or neoadjuvant chemotherapy, 5-year OS was 77%, and DFS at this interval was 45%. In a separate series of 39 patients, 61.8% of patients received a combination of chemotherapy, endocrine therapy and radiation after surgery, while 7.7% of patients received only hormonal therapy and radiation [89]. In this experience, receipt of radiation therapy was not associated with a benefit in DFS or OS.

8. Conclusions

Given the documented rise in MBC incidence in two large registry analyses, developing a more thorough understanding of this disease is of critical importance [3,11]. The receptor profile of MBC (with increased ER, PR and HER2 expression) makes it an attractive candidate for endocrine and HER2-directed therapies [40]. Furthermore, ongoing studies to define the molecular and genetic profile of MBC may yield other relevant biomarkers and therapeutic targets. A challenge that lies ahead in the research community is uniting efforts for the development of prospective trials to address this population. Without a concerted effort, the literature pertaining to MBC will remain a collection of retrospective series and pilot studies. Efforts to develop randomized, prospective studies within cooperative groups and other clinical trial consortia are essential.

Provenance and peer review

Commissioned and externally peer reviewed.

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