Current state of surgical management for male breast cancer

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Abstract: Management guidelines for male breast cancer have long been extrapolated from those for female breast cancer, which are based on large, randomised-controlled trials. While there are no randomised-controlled trials for male breast cancer management mainly due to the rarity of the disease, the only type of evidence available comes from retrospective studies, subject to selection biases and small sample sizes. Male breast cancer, while similar to female breast cancer in many respects, has some important differences that can affect management choices. Most cancers are oestrogen and progesterone receptor positive, and usually more advanced at presentation than female breast cancer. This is likely due to less breast parenchyma in male patients and delay to diagnosis. The classical management option for male patients with breast cancer is mastectomy, due to small tumour-to-breast ratio and often central position of the tumour. Breast conserving surgery is still useful in selected cases and has similar outcomes when compared to mastectomies in these patients. For patients with clinically negative lymph nodes, sentinel lymph node biopsy offers the same prognosis as axillary lymph node dissection, but with less associated morbidity. Endocrine therapy is of particular use, due to high levels of receptor positivity. Adjuvant endocrine therapy seems to significantly improve overall survival of male patients with breast cancer and while no prospective evidence exists for neoadjuvant hormonal therapy, there is hope that this is a useful management option as well. Radiotherapy is also useful in an adjuvant setting, particularly when combined with endocrine therapy. Better identification of patients, less delay from presentation to diagnosis and more collaborative efforts are key in improving the management, prognosis and outcomes of patients with male breast cancer.

Keywords: Male breast cancer (MBC); mastectomy; breast-conserving surgery; sentinel node biopsy; adjuvant therapy; neoadjuvant therapy

Introduction

Male breast cancer (MBC) is a rare type of breast cancer comprising 0.5–1% (1,2) of all breast cancers. Its management guidelines are based on breast cancer in women. There have yet to be any randomised-controlled trials (RCTs) for the management of MBC (3) and most of our information is derived from retrospective studies, which have been limited by small sample sizes. While collaborative efforts have been successful in creating a more reliable picture (2,4,5), robust scientific evidence is still needed for how to manage these patients. This review considers the current evidence for the surgical management of MBC and is meant to complement recent similar publications (3) in trying to build the picture of the current state of MBC management, while encouraging future research.

Male breast cancer—an entity of its own?

There are roughly 390 men diagnosed with MBC every

year in the UK and some reports indicate that MBC rates seem to be increasing (6,7). How much of this is due to a real increase in incidence or due to enhanced capturing in databases (e.g., the Surveillance, Epidemiology and End Results - SEER dataset) is not clear yet (8). The median age of presentation has been reported to be around 65–69 years of age, slightly higher than in female breast cancer (FBC). Additionally, age-specific incidence seems to be similar between the two (2,4). Risk factors for MBC include Klinefelter's syndrome, BRCA mutations, gynaecomastia, increased BMI, diabetes, cirrhosis, cryptorchidism and exogenous use of oestrogens (e.g., for prostate cancer or in transgender patients). Black men are also more likely to develop it than white men (1,9-11). The most common histological type of MBC is invasive ductal carcinoma (84.8–90%) (4,12), while the most common subtype of MBC is luminal A (81–98%) (13,14). MBC also has disproportionately higher rates of oestrogen and progesterone receptor positivity when compared to FBC (92–99% in MBC vs. 78% in FBC) (4,15). These rates have been found to be similar between men and matched post-menopausal females (16).

Surgical management—what is the evidence?

It is difficult to determine robust management guidelines for MBC—in the absence of prospective randomised controlled trials—the best currently-available evidence stems from retrospective studies.

Breast conserving surgery (BCS) is a commonly used and effective treatment for FBC (17,18) but in MBC breast cancer it is rarely used. In a large American analysis of the SEER database performed by Fields et al. (2), 4,276 male breast cancers were identified and BCS was performed in only 9.7% of males, whilst mastectomies were performed in 67.5%. Another SEER study performed by Cloyd et al. (5) showed that out of 5,425 males that underwent treatment for MBC, 86.8% underwent mastectomy and 13.2% underwent BCS. The results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Programme (4) published by Cardoso et al. paint an even more dramatic picture: only 3.1% of total number of patients with M0 state underwent BCS, while 75.3% had modified radical mastectomy (surgical data was missing for 21.4% of patients). Mastectomy is therefore the most commonly used surgical procedure for MBC. However, an increase in rates of performing BCS has been reported by both Cardoso et al. and Cloyd et al. from

2.2% in 1990–1995 to 2.8% in 2006–2010 and 10.6% in 1983–1986 to 15.1% in 2007–2009 respectively. Several studies have noted that BCS is actually equally effective when compared to mastectomy in the management of early-stage MBC. Zaenger et al. compared the outcomes of 1,777 patients with early-stage male breast cancer and found that, while only 17% of patients had BCS, the 5-year cause-specific survival between the group of patients undergoing BCS and the ones undergoing mastectomy (either modified radical or simple) was very similar: 100% and 97.3% respectively (19). In addition to this, Leone et al. looked at the overall survival for 1263 T1a,b,c N0M0 patients from the SEER programme (20). They found there is no significant difference in the overall survival between BCS and mastectomy. Fields et al. also looked at the comparison between BCS and mastectomy in localised disease and found no difference in cause-specific survival between patients receiving lumpectomy and radiotherapy versus mastectomy (98.8% vs. 95.5% respectively) (2). There is also evidence suggesting decreased morbidity following BCS, when compared to mastectomy. In a smaller study of 42 patients (21), Fogh et al. compared the rates of tissue fibrosis, arm oedema and shoulder range of movement between groups undergoing mastectomies (total or modified radical) and the group undergoing BCS. The latter group had decreased complication rates (13%, 0% and 0% respectively) when compared to either modified radical mastectomies (13%, 23% and 27% respectively) or total mastectomy (25%, 0% and 50%) (21).

Even in later stages, surgical management has been shown to be a beneficial form of treatment. Looking at 439 patients with stage IV MBC in the SEER programme, Muzaffar et al. (8) compared the medial overall survival between those receiving primary tumour surgery (in the form of simple, radical, modified radical and partial mastectomy) and those not receiving any form of surgery. There was a significant increase in mortality in patients not undergoing surgery (hazard ratio =1.81; 95% CI, 1.42–2.31; P<0.0001).

Axillary lymph node dissection versus sentinel lymph node biopsy

An important question to consider about axillary procedures in male breast cancer is whether to default to axillary lymph node dissections or to consider sentinel lymph node biopsies more often. Axillary lymph node

dissection (ALND) reduces the mortality of breast cancer patients (22,23), but it can also be associated with significant morbidity and complications (24,25). Therefore, more conservative procedures, if appropriate, are desirable. Several retrospective studies (25-28) have shown that sentinel lymph node biopsy (SLNB) is a reliable and safe procedure in male patients with clinically node-negative disease and can be used to further guide adjuvant management of MBC. Leone *et al.* also looked at the impact of the number of analysed lymph nodes during axillary lymph node examination on overall survival in a cohort of node-negative patients. There was no difference in overall survival between patients receiving sentinel lymph node biopsy (1–5 lymph nodes examined) and axillary dissection (>5 lymph node examined). There was however significantly poorer overall survival if no lymph nodes were examined (20). In keeping with these findings, a significant trend favouring SLNB to ALND has been reported in the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Programme results across 1990–2010 (4).

Adjuvant and neoadjuvant therapy

Endocrine therapy using tamoxifen or aromatase inhibitors is an established adjuvant treatment for female breast cancer. It thus follows that questions regarding their efficacy in MBC needed to be addressed. In a retrospective study using the SEER dataset (29), Harlan *et al.* compared the effect of hormonal therapy on mortality in men with ER positive/borderline tumours; they found that tamoxifen was associated with significant reduction in cancer mortality (hazard ratio 0.04; 95% CI: 0.1–0.99), whereas aromatase inhibitor (AI) use did not decrease mortality (hazard ratio 1.2; 95% CI: 0.4–3.8) when compared to no therapy. In a similar retrospective study of 257 men with ER positive breast cancer (30), Eggemann *et al.* showed that overall survival was significantly increased in the group taking tamoxifen when compared to the group taking AIs. There is thus use for tamoxifen in the adjuvant management of male breast cancer, while aromatase inhibitors do not seem as effective. Also, given the very high rates of receptor positivity among MBC, hormonal therapy is a very promising treatment option indeed. Unfortunately, due to small sample sizes, the limitations of retrospective studies and lack of randomised-controlled trials, it is difficult to give a definitive answer. The lack of prospective studies addressing the use of hormonal therapy in a neoadjuvant setting illustrates its minimal usage. The current evidence

regarding adjuvant tamoxifen may suggest it might be appropriate as a neoadjuvant agent as well (3), formal evaluation in locally advanced cases is needed.

Radiotherapy is another adjuvant option imported from female breast cancer management and it is significantly underutilised in MBC (2,31). Several retrospective studies have looked at the efficiency of adjuvant radiotherapy and have found that it can increase overall survival in stage I/III cancers, in both node positive and negative disease and in patients with close or unknown margins (32-36). It has been suggested that the indications for adjuvant radiotherapy in MBC should be the same as those in female breast cancer and should include all patients undergoing BCS and in mastectomy patients if advanced T stage and/or metastatic lymph nodes (35,37,38). Accordingly, the European Oncology Institute in Milan proposes use of post-mastectomy adjuvant radiotherapy in cases where the tumour is >1 cm in size and/or if there is >1 metastatic lymph node (38). Additionally, the use of post-mastectomy adjuvant radiotherapy in patients with high-risk T2 and positive lymph nodes has been shown to reduce locoregional recurrence (35).

Initial presentation

When matched by stage, male breast cancer has similar (or even better) outcome than female breast cancer (39,40). Despite this, male breast cancer has poorer prognosis and tends to be more advanced at diagnosis than its female counterpart (41,42). Reasons for this include delay in diagnosis and presentation, less breast parenchyma in men and a general lack of public awareness (8,43,44). Delay between onset of symptomatology and diagnosis has been estimated to be >10 months (45). This shows a concerning picture of the state of MBC being initially diagnosed. Faster diagnosis with less delay is associated with lower stage (45) so striving to improve this is likely to have a positive impact on outcomes and survival.

Men are most likely to present with a sub-areolar mass (46) and are most at risk of having lymphovascular invasion and nipple involvement (47). Mammography and ultrasound, together with fine needle aspiration have been shown to be of use in diagnosing breast cancer in men in a few studies, limited though by their small sample sizes (48,49).

While screening might not be appropriate in the general population due to the rarity of this condition, screening of target groups at risk might prove beneficial in diagnosing and treating patients with MBC. Overall, improved and

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streamlined diagnosis, with fewer delays are likely to improve the outcomes for MBC, particularly as advanced stage is clearly associated with poorer outcomes and increased mortality (50).

Conclusions

Management of male breast cancer is largely based on existing guidelines for female breast cancer. The MBC-specific evidence we have is derived from retrospective studies, flawed by small sample sizes and vulnerable to confounding factors and selection biases. The most reliable data we have stems from cooperative efforts with large samples. As proper randomised-controlled trials are very difficult to organise due to the scarcity of cases, large, multinational collaborative efforts are the likely way forward (3).

While mastectomy is the main surgical option for MBC, breast-conserving surgery has been gaining more popularity. Unfortunately, use of breast-conserving surgery in MBC is limited as most breast cancers in men occur centrally, with a high tumour-to-breast ratio and tend to be more advanced at presentation (4,37,43). Earlier diagnosis may allow patients to be treated at an earlier stage and thus might favour more conservative approaches, such as breast-conserving surgery using oncoplastic techniques and SLNB with improved outcomes.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Ruddy KJ, Winer EP. Male breast cancer: risk factors, biology, diagnosis, treatment, and survivorship. Ann Oncol 2013;24:1434-43.
2. Fields EC, DeWitt P, Fisher CM, et al. Management of Male Breast Cancer in the United States: A Surveillance, Epidemiology and End Results Analysis. Int J Radiat Oncol Biol Phys 2013;87:747-52.
3. Fentiman IS. Surgical options for male breast cancer. Breast Cancer Res Treat 2018;172:539-44.
4. Cardoso F, Bartlett JMS, Slaets L, et al. Characterization of male breast cancer: Results of the EORTC 10085/ TBCRC/BIG/NABCG International Male Breast Cancer Program. Ann Oncol 2018;29:405-17.
5. Cloyd JM, Hernandez-Boussard T, Wapnir IL. Outcomes of Partial Mastectomy in Male Breast Cancer Patients: Analysis of SEER, 1983-2009. Ann Surg Oncol 2013;20:1545-50.
6. Male breast cancer | Cancer Research UK [cited 2019 Feb 7]. Available online: https://www.cancerresearchuk.org/ about-cancer/breast-cancer/stages-types-grades/types/ male-breast-cancer
7. Giordano SH, Cohen DS, Buzdar AU, et al. Breast carcinoma in men. Cancer 2004;101:51-7.
8. Muzaffar M, Kachare S, Vohra N. Impact of Primary Tumor Surgery in Stage IV Male Breast Cancer. Clin Breast Cancer 2017;17:e143-9.
9. Brinton LA, Cook MB, McCormack V, et al. Anthropometric and Hormonal Risk Factors for Male Breast Cancer: Male Breast Cancer Pooling Project Results. J Natl Cancer Inst 2014;106:djt465.
10. Ewertz M, Holmberg L, Tretli S, et al. Risk factors for male breast cancer--a case-control study from Scandinavia. Acta Oncol 2001;40:467-71.
11. Korde LA, Zujewski JA, Kamin L, et al. Multidisciplinary meeting on male breast cancer: summary and research recommendations. J Clin Oncol 2010;28:2114-22.
12. Fentiman IS, Fourquet A, Hortobagyi GN. Male breast cancer. Lancet 2006;367:595-604.
13. Nilsson C, Johansson I, Ahlin C, et al. Molecular subtyping of male breast cancer using alternative definitions and its prognostic impact. Acta Oncol 2013;52:102-9.
14. Shaaban AM, Ball GR, Brannan RA, et al. A comparative biomarker study of 514 matched cases of male and female breast cancer reveals gender-specific biological differences. Breast Cancer Res Treat 2012;133:949-58.
15. Anderson WF, Jatoi I, Tse J, Rosenberg PS. Male Breast Cancer: A Population-Based Comparison With Female Breast Cancer. J Clin Oncol 2010;28:232-9.
16. Meijer-van Gelder ME, Look MP, Bolt-de Vries J, et al. Clinical relevance of biologic factors in male breast cancer. Breast Cancer Res Treat 2001;68:249-60.
17. Fisher B, Anderson S, Bryant J, et al. Twenty-Year Follow-up of a Randomized Trial Comparing Total Mastectomy, Lumpectomy, and Lumpectomy plus Irradiation for the Treatment of Invasive Breast Cancer. N Engl J Med 2002;347:1233-41.
18. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-Year Follow-up of a Randomized Study Comparing Breast-

Conserving Surgery with Radical Mastectomy for Early Breast Cancer. N Engl J Med 2002;347:1227-32.

19. Zaenger D, Rabatic BM, Dasher B, et al. Is Breast Conserving Therapy a Safe Modality for Early-Stage Male Breast Cancer? Clin Breast Cancer 2016;16:101-4.

20. Leone JP, Leone J, Zwenger AO, et al. Locoregional treatment and overall survival of men with T1a,b,cN0M0 breast cancer: A population-based study. Eur J Cancer 2017;71:7-14.

21. Fogh S, Kachnic LA, Goldberg SI, et al. Localized therapy for male breast cancer: functional advantages with comparable outcomes using breast conservation. Clin Breast Cancer 2013;13:344-9.

22. Giuliano AE, Ballman KV, McCall L, et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis. JAMA 2017;318:918.

23. Huang TW, Kuo KN, Chen KH, et al. Recommendation for axillary lymph node dissection in women with early breast cancer and sentinel node metastasis: A systematic review and meta-analysis of randomized controlled trials using the GRADE system. Int J Surg 2016;34:73-80.

24. Madsen RJ, Esmonde NO, Ramsey KL, et al. Axillary Lymph Node Dissection Is a Risk Factor for Major Complications After Immediate Breast Reconstruction. Ann Plast Surg 2016;77:513-6.

25. Maráz R, Boross G, Pap-Szekeres J, et al. The role of sentinel node biopsy in male breast cancer. Breast Cancer 2016;23:85-91.

26. De Cicco C, Baio SM, Veronesi P, et al. Sentinel node biopsy in male breast cancer. Nucl Med Commun 2004;25:139-43.

27. Cimmino VM, Degnim AC, Sabel MS, et al. Efficacy of sentinel lymph node biopsy in male breast cancer. J Surg Oncol 2004;86:74-7.

28. Martin-Marcuartu JJ, Alvarez-Perez RM, Sousa Vaquero JM, et al. Biopsia selectiva del ganglio centinela en el cáncer de mama del varón. Rev Esp Med Nucl Imagen Mol 2018;37:146-50.

29. Harlan LC, Zujewski JA, Goodman MT, et al. Breast cancer in men in the United States: a population-based study of diagnosis, treatment, and survival. Cancer 2010;116:3558-68.

30. Eggemann H, Ignatov A, Smith BJ, et al. Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. Breast Cancer Res Treat 2013;137:465-70.

31. Chakravarthy A, Kim CR. Post-mastectomy radiation in male breast cancer. Radiother Oncol 2002;65:99-103.

32. Madden NA, Macdonald OK, Call JA, et al. Radiotherapy and Male Breast Cancer. Am J Clin Oncol 2016;39:458-62.

33. Stranzl H, Mayer R, Quehenberger F, et al. Adjuvant radiotherapy in male breast cancer. Radiother Oncol 1999;53:29-35.

34. Eggemann H, Ignatov A, Stabenow R, et al. Male breast cancer: 20-year survival data for post-mastectomy radiotherapy. Breast Care (Basel) 2013;8:270-5.

35. Yu E, Suzuki H, Younus J, et al. The impact of post-mastectomy radiation therapy on male breast cancer patients--a case series. Int J Radiat Oncol Biol Phys 2012;82:696-700.

36. Jardel P, Vignot S, Cutuli B, et al. Should Adjuvant Radiation Therapy Be Systematically Proposed for Male Breast Cancer? A Systematic Review. Anticancer Res 2018;38:23-31.

37. Fogh S, Hirsch AE, Goldberg SI, et al. Use of Tamoxifen With Postsurgical Irradiation May Improve Survival in Estrogen and Progesterone Receptor-Positive Male Breast Cancer. Clin Breast Cancer 2011;11:39-45.

38. Gennari R, Curigliano G, Jereczek-Fossa BA, et al. Male breast cancer: a special therapeutic problem. Anything new? (Review). Int J Oncol 2004;24:663-70.

39. Marchal F, Salou M, Marchal C, et al. Men With Breast Cancer Have Same Disease-Specific and Event-Free Survival as Women. Ann Surg Oncol 2009;16:972-8.

40. Miao H, Verkooijen HM, Chia KS, et al. Incidence and outcome of male breast cancer: an international population-based study. J Clin Oncol 2011;29:4381-6.

41. Tajima N, Tsukuma H, Oshima A. Descriptive epidemiology of male breast cancer in Osaka, Japan. J Epidemiol 2001;11:1-7.

42. Gnerlich JL, Deshpande AD, Jeffe DB, et al. Poorer survival outcomes for male breast cancer compared with female breast cancer may be attributable to in-stage migration. Ann Surg Oncol 2011;18:1837-44.

43. Ahmed A, Ukwenya Y, Abdullahi A, et al. Management and outcomes of male breast cancer in zaria, Nigeria. Int J Breast Cancer 2012;2012:845143.

44. Uslukaya Ö, Gümüş M, Gümüş H, et al. The Management and Outcomes of Male Breast Cancer. J Breast Health 2016;12:165-70.

45. Culell P, Solernou L, Tarazona J, et al. Male breast cancer: a multicentric study. Breast J 2007;13:213-5.

46. Jamal S, Mamoon N, Mushtaq S, et al. Carcinoma of the male breast: a study of 141 cases from northern Pakistan.

Asian Pac J Cancer Prev 2006;7:119-21.

47. Joshi MG, Lee AK, Loda M, et al. Male breast carcinoma: an evaluation of prognostic factors contributing to a poorer outcome. Cancer 1996;77:490-8.

48. Doyle S, Steel J, Porter G. Imaging male breast cancer. Clin Radiol 2011;66:1079-85.

49. Sneige N, Holder PD, Katz RL, et al. Fine-needle

aspiration cytology of the male breast in a cancer center. Diagn Cytopathol 1993;9:691-7.

50. Scott-Conner CE, Jochimsen PR, Menck HR, et al. An analysis of male and female breast cancer treatment and survival among demographically identical pairs of patients. Surgery 1999;126:775-80; discussion 780-1.