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Review

Should Adjuvant Radiation Therapy Be Systematically Proposed for Male Breast Cancer? A Systematic Review

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Abstract. *Background: Guidelines for radiotherapy in male breast cancer (MBC) are lacking. Some extrapolate the results from female breast cancer trials, while others advocate systematic adjuvant irradiation. We evaluated clinical practices and outcomes with respect to radiation therapy in MBC treated with locoregional irradiation in the adjuvant setting using a systematic literature review. Material and Methods: We included studies with data about adjuvant radiotherapy published between 1984 and 2017 and including at least 40 patients. Results: We found 29 retrospective series, 10,065 men were diagnosed with breast cancer; 3-100% (mean=54%) received adjuvant radiotherapy. Tumor size and nodal involvement were the strongest prognostic factors. Approximatively half of all cases had nodal metastases. Radiation therapy improved locoregional control in six series, overall survival in three and distant metastasis-free survival in one. Conclusion: MBC is diagnosed at a highly advanced stage and may be linked with poorer outcomes. Adjuvant radiation therapy must, at least, be proposed to men with positive nodes. Despite the large number of cases gathered here, arguments for radiotherapy in other prognostic subgroups (especially in pN0) may exist but are not well supported.*

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Breast cancer in males is infrequent, representing 1% of all breast carcinomas, and less than 1% of all male cancers (1, 2), even if its incidence seems to be increasing (3-7). All studies regarding male breast cancer (MBC) are retrospective and specific recommendations are sparse. The general management of non-metastatic MBC is usually based on guidelines for female breast cancer (FBC). Surgery, chemotherapy and hormonal therapy are based on classical prognostic factors. After mastectomy, which represents the majority of cases, locoregional irradiation for MBC remains controversial. Some institutions recommend systematic post-mastectomy irradiation considering that MBC is intrinsically more aggressive than FBC and that the ratio of tumor size to gland could lead to minimal surgical margins; others suggest that the natural history of MBC resembles that of post-menopausal female breast cancer and that the aggressiveness is biased by a more advanced stage at diagnosis (1, 2, 4). Institutions base their recommendations for MBC based on data established for females. We evaluated clinical practices and outcomes with respect to radiation therapy in MBC treated with locoregional irradiation in the adjuvant setting using a systematic literature review.

Materials and Methods

Our systematic review of the literature was based on the Preferred Reporting Items for Systematic Reviews and meta-Analysis (PRISMA) recommendations (http://www.prisma-statement.org/). Data were selected from a search on PubMed during the period 1976 to 2017 and from references in identified articles, using the following search terms: “breast cancer”, “men”, “male”, “radiotherapy”; articles published in English or French were included. Relevant articles were selected with the following inclusion criteria: non metastatic MBC, an original study with more

Table I. *Studies meeting the inclusion criteria.*

Country	Year	First author (Ref.)	n	Era	Follow-up	RT/ no RT	Men/ women
Canada	1984	Erlichman *et al.* (8)	85	1967-1981 (14 years)	NR	Yes	No
USA	1992	Borgen *et al.* (9)	104	1975-1990 (15 years)	Median 67 months (range=6 months-15 years)	No	No
Spain	1994	Izquierdo *et al.* (10)	50	1964-1990 (26 years)	Median 65 months (range=3-185 months)	No	No
UK	1994	Lartigau *et al.* (11)	65	1968-1988 (20 years)	Median 54 months	No	No
France	1995	Cutuli *et al.* (12)	382	1960-1986 (26 years)	Median 74 months	Yes	No
Austria	1995	Stierer *et al.* (13)	169	1970-1991 (21 years)	Median 51 months (range=12-192 months)	No	No
UK	1997	Willsher *et al.* (14)	41	1974-1994 (20 years)	Median 42 months	Yes	Yes
Turkey	1998	Yildirim *et al.* (15)	121	1972-1994 (22 years)	Median 29 months (range=3-146 months)	Yes	No
USA	2002	Chakravarthy *et al.* (16)	44	1967-1995 (28 years)	Median 96 months (range=8-246 months)	Yes	No
Canada	2005	McDonald *et al.* (21)	159	1989-1998 (9 years)	Median 8.4 years (range=4.5-14.3 years)	No	Yes
Turkey	2006	Atahan *et al.* (17)	42	1994-2001 (7 years)	Median 29 months (range=4.5-118 months)	No	No
France	2008	Tunon de lara *et al.* (19)	44	1980-2004 (24 years)	Median 136months (range=125-146 months)	No	No
China	2010	Zhou *et al.* (35)	70	1968-2009 (41 years)	Median 55 months (range=3-391 months)	Yes	No
France	2010	Cutuli *et al.* (20)	489	1990-2005 (15 years)	Median 58 months	No	No
Finland	2010	Liukkonen *et al.* (22)	58	1981-2006 (25 years)	Median 5 years (1 month -24 years)	No	No
Sweden	2011	Nilsson *et al.* (23)	99	1993-2007 (14 years)	Median 4.1years	No	Yes
Turkey	2012	Arslan *et al.* (24)	118	1986-2009 (23 years)	Median 40.9 months	Yes	No
Canada	2012	Yu *et al.* (25)	75	1977-2006 (29 years)	Median 46 months (range=1-225 months)	Yes	No
France	2012	Dabakuyo *et al.* (26)	75	1982-2008 (26 years)	Median 8 years (range=5-9 years)	Yes	No
Germany	2012	Müller *et al.* (27)	40	1982-2007 (25 years)	Median 47 months	No	Yes
USA	2013	Moten *et al.* (28)	156	1988-2008 (20 years)	NR	No	Yes
USA	2013	Fogh *et al.* (29)	42	1990-2003 (13 years)	Median 8 years (range=3-18 years)	No	No
Germany	2013	Eggeman *et al.* (30)	664	1970-1989 (19 years)	Mean 26.2 years (19-38 years)	Yes	No
Italy	2013	Meattini *et al.* (31)	60	1971-2011 (40 years)	Median 8.9 years (range=0.6-20years)	Yes	No
USA	2013	Fields *et al.* (6)	4276	1973-2008 (35 years)	NR	Yes	Yes
Canada	2014	Ruschton *et al.* (32)	72	1981-2009 (28 years)	Median 45 months (range=2-204 months)	No	Yes
USA	2014	Madden *et al.* (34)	1337	1983-2002 (19 years)	Median 7.3 years (range=1 month-25 years)	Yes	No
France	2015	Oger *et al.* (33)	95	2000-2010 (10 years)	Median 45 months (range=7-132 months)	No	No

n: Number of men; NR: not reported. The two last columns indicate whether the authors compared outcomes by whether radiotherapy was given or not and between men and women.

than 40 patients receiving irradiation, inclusions beginning after 1960. full text availability and details on radiotherapy procedures (articles were excluded if radiotherapy was not specifically studied). Repeated publications were only selected once. Characteristics of MBC and treatment modalities were extracted. Impact on local tumor control and survival was estimated.

Results

Relevant articles. One hundred and seventy-one articles were identified and assessed. Twenty-nine of them met the inclusion criteria (Figure 1 and Table I), involving 10,965 men diagnosed with breast cancer (6, 8-35). No prospective study had been published. Average follow-up was between 7 and 314 months (median=60 months). The number of patients per study was between 40 and 664 (mean=82), except for three studies utilizing national databases (with 4,276, 1,933, and 1,337 patients, respectively) (6,18, 34). Patients were treated during the period 1960-2013. Mean inclusion time was 22 years (range=7-41 years). Males were matched with females in seven of the series. Comparisons of outcomes with or without post-mastectomy radiotherapy were available in 14 of the articles reviewed.

MBC characteristics. Clinical and pathological characteristics of patients with MBC as described in selected publications are presented in Table II. The median age was 63 years (range of the median=55 to 68 years). Pre-existing comorbidities were frequent in this population: 42% of the patients had one or more chronic disease, increasing with age (20, 21, 30). Tunon de Lara *et al.* showed that 57% (20/35 patients for whom the body mass index could be evaluated) were overweight (19).

The most tumor common type was invasive ductal carcinoma (80-95%), followed by ductal carcinoma *in situ* (5-10%) (36). Estrogen receptor (ER) was expressed in 88% of cases. The expression of human epidermal growth factor receptor 2 (HER2) was reported in the most recent studies and estimated as positive in 15% of cases. Studies were not

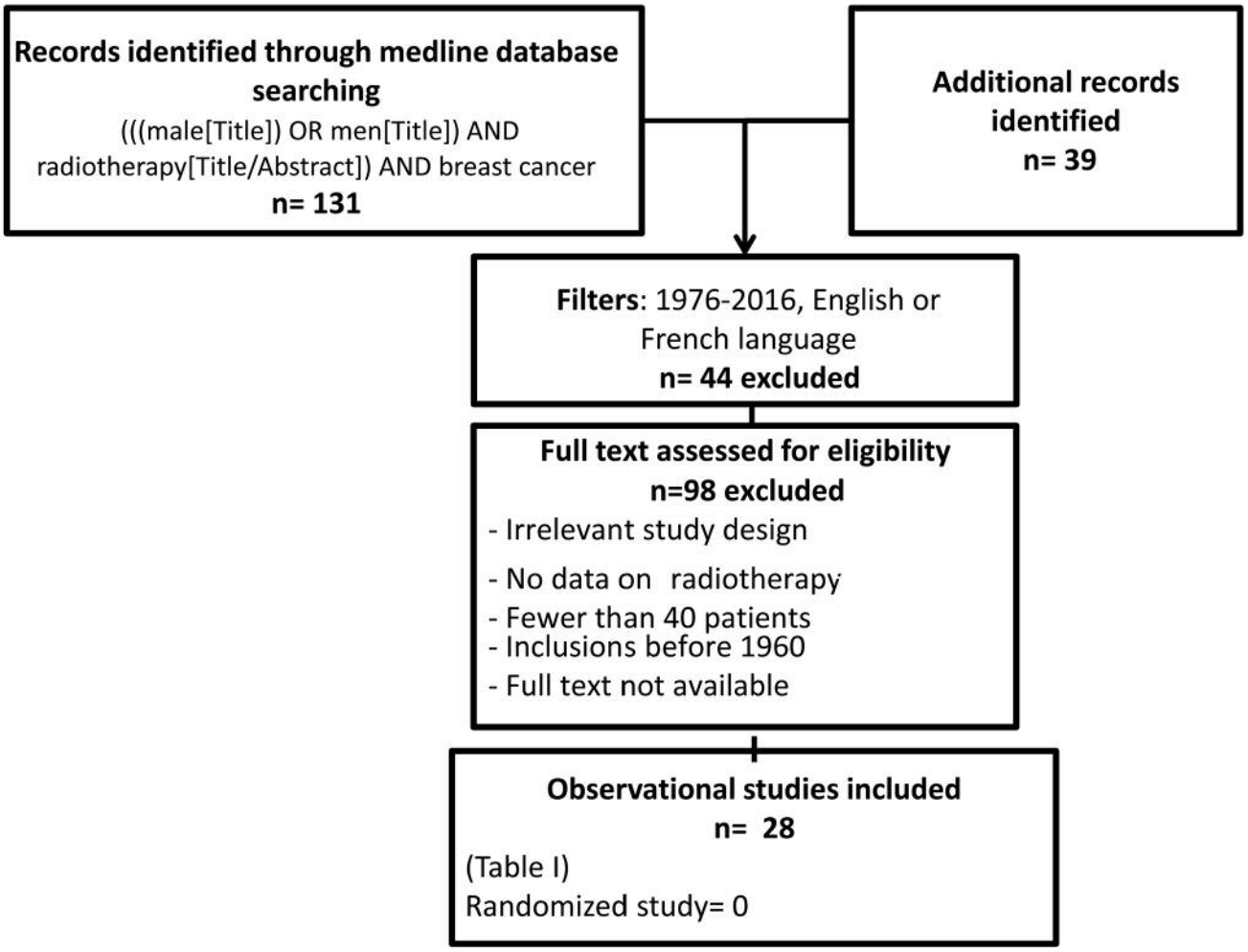

Figure 1. *Study design*.

unequivocal concerning the histological grade distribution in males in comparison with females; the largest comparative study by Fields *et al*. found a similar distribution of grades. In their study, 23% of tumors were pT4 and 50% presented nodal involvement. A large tumor size was associated with poorer outcomes (6). Lartigau *et al*. reported a significant difference in 10-year disease-specific survival between those with T4 and those with T1 tumors (32% *versus* 87%, p=0.001) (11); Cutuli *et al*. reported 10-year disease-specific survival rates for those with T0-T1, T2 and T3-T4 of 81%, 80% and 69%,respectively (20). Lymph node involvement was a strong prognostic factor in most MBC studies (15, 31,34, 36, 37). The 10-year survival was 28% when lymph nodes were not involved *versus* 58% when involved (12). Such data were reported before the systematic use of sentinel node biopsy in females. Omission of axillary dissection led to increased regional nodal relapses rates in MBC (12, 13).

In our analysis, eight studies were before 1990 (8-13, 16, 30), eight after (17, 18, 20-24, 29, 33), and the remaining study covered longer periods. The frequency of T4 stage cases tended to decrease with time: 26% (range=11-71%) *versus* 13% (range=10-20%) on average between these two time periods. The percentage of involved nodes was 48% (range=35-57%) in the oldest series and 43% (range=31-62%) in the newest.

Surgery. Surgical approaches were similar to those used in FBC. Radical mastectomy was the main surgical procedure until the 1970s. The studies showed a progressive decrease in the rate of radical mastectomy over the past several decades, being replaced by modified radical mastectomy, with equivalent general locoregional relapse rates (12, 34, 35). Rates of patients who underwent breast partial surgery varied between 5 and 25% (mean=7%). Partial mastectomies were

more likely proposed in a palliative context in older men with advanced disease, even though they could also have been performed in those with limited disease for better cosmetic, functional and psychological tolerance (29). Surgical procedures for axillary nodes (dissection, sentinel node biopsy or both) were performed in 45% to 100% in the whole series of patients (mean=91%). However, strictly speaking modified radical mastectomy includes an axillary dissection.

Adjuvant systemic treatments. Adjuvant hormonal treatment and chemotherapy has increased over the past decades (24, 26, 36, 38). The rate of patients who received chemotherapy varied between 3 and 85% (mean=26%) and hormonal therapy between 7 and 92% (mean=45%). In a French series including patients between 1990 and 2005, hormonal treatment was delivered in 72% of the cases (tamoxifen represented 85% and aromatase inhibitors, 12%) and increased over time (57%, 74% and 82% in 1988-1995, 1996-2000 and 2001-2005, respectively, $p<0.0001$); adjuvant chemotherapy was delivered in 34% of the cases with an anthracycline-based regimen in 73% (25% in 1988-1995 and 37% in 1996-2005, $p=0.029$) (20). In a matched series in the United Kingdom (period 1963-2006; males and females were matched according to age, tumor size, nodal status, margins, and treatments), chemotherapy was given in 16% of the males and 45.5% of the females, although nodal invasion accounted for 51% of MBC cases and 56% of FBC cases (39).

Table II. *Clinical and pathological characteristics of male breast cancer.*

Characteristic	Mean	Range
Number of patients	9,032	41-4276
Age at diagnosis, years	63	24-97
Diagnosis before 50 years old	13%	10.5-16%
Delay before treatment	6 Months	3-13 Months
Most frequent tumor location: Retroareolar	76%	66-86%
Multi-centric/focal	–	(Two reports: 1 and 9%)
Inflammatory breast	4%	0-8%
Tumor size	2.25cm	1.8-3cm
Invasive ductal carcinoma	90%	80-100%
Grade 3	28%	12-70%
ER+	88%	77-100%
pT1	37%	3-77%
pT2	34%	11-56%
pT3	12%	2-42%
pT4	23%	10-71%
pN+	50%	31-74%
Including pN2, pN3	18%	2-43%

ER+: Estrogen receptor expression. Mean numbers were calculated from all available series. Conclusions about human epidermal growth factor receptor 2 (HER2) cannot be drawn since its evaluation was generally not performed before 2005; for instance, HER/2neu was overexpressed in 7% of MBC in Oger *et al*. (24), 23% in Arslan *et al*. (33).

Adjuvant radiotherapy. The utilization of postoperative radiotherapy in males varied between 3% and 100% (mean=64%). The choice of target volumes (chest wall, nodal areas, and boost) was not clearly stated in most studies. In a cohort of 75 patients reported by Yu *et al*., radiotherapy was indicated for the chest wall after mastectomy (with or without supraclavicular/axillary/internal mammary nodes) in high-risk patients with close/positive margins, positive nodes and pT3 (25). MacDonald *et al*. showed that radiotherapy was almost six times more likely given to males than females (even with the exclusion of T4 cases). Withholding radiotherapy was either advocated in females with good prognostic factors or males with poor performance status (21). Indications and techniques of radiation therapy were not systematically reported and varied depending on authors/countries and periods (with the use of cobalt and orthovoltage in earlier periods) (6, 20, 35). Müller *et al*. mentioned an electron beam rotational technique for the chest wall (27). Tangential fields were adjusted seeking to include more nodal tissue (first axillary area or internal mammary nodes) (27, 40). Total dose was around 50 Gy in 25 fractions in most studies. Lower total doses or hypofractionation in subgroups of elderly patients were not identified. Younger patients were more likely to receive adjuvant radiotherapy (30). Some authors used boost to the chest wall, for incomplete resection or tumor classified as T4 (11, 13, 27). After partial mastectomy, radiation therapy was not systematically given. In a large American database (1983-2009), of the 718 males that underwent lumpectomy, 35.4% received adjuvant radiation therapy (41). In Scott-Conner *et al*.'s study matching 3627 males and females during the period 1985-1994 (using United States national database), the minority of males who underwent lumpectomy were less likely to receive adjuvant radiation therapy than females (42).

Impact of radiotherapy on local control and overall survival. The influence of radiotherapy on locoregional control is reported in Table III. Eggeman *et al*. found a statistical benefit in overall survival rates between patients with stage III disease treated by adjuvant radiotherapy compared to those without (10-year overall survival=26.4% *vs*. 11.9%), whereas it was not significant in the entire group (30). On the other hand, using a national database, Madden *et al*. showed a significant survival benefit for post mastectomy radiotherapy in stage I with a positive trend for the other stages, without improved specific survival (1,337 patients). Adjuvant radiotherapy for tumors larger than 5 cm tended to improve overall survival and relative survival in this study (34). Patients who received adjuvant radiotherapy with N2 and N3 disease had a trend towards an increase in overall and specific survival (in this cohort, 25% of patients underwent

Table III. *Influence of radiotherapy on locoregional control of male breast cancer.*

Country	Author, year (Ref)	Era	n	Partial mastectomy	EBRT	Locoregional failure*		Distant failure	OS (5-year)
						No EBRT	EBRT		
Canada	Erlichman *et al*., 1984 (8)	1967-1981	85	7%	67%	LR (5-year): 31%	LR (5-year) ~26%‡	~52%‡	~64%‡ (No EBRT) ~52%‡ (EBRT)
France	Cutuli *et al*., 1995 (12)	1960-1986	373	13%	51%	LR:11.5% RR:5.5%	LR:4.7% RR:2.1%	~40%‡	~65%‡
UK	Willsher *et al*., 1997 (14)	1974-1994	41	7%	25%	LR:27% RR:47%**	LR:10% RR:20%	34%	~55%‡
USA	Chakra-varthy *et al*., 2002 (16)	1967-1995	44	4%	30%	1 Patient (pN0)	2 Patients (pN2)	14%	75%
Canada	Yu *et al*., 2012 (25)	1977-2006	75	4%	61%	24%	4%	37% (EBRT) vs. 7% (no EBRT)	74%
Italy	Meattini *et al*., 2013 (31)	1971-2011	60	3%	43%	LR:12%	LR:4% (significant)	27%	(8.9 years) 53%

LR: Local recurrence (chest wall), RR: regional recurrence (axillary or supraclavicular nodes), EBRT: external-beam radiation therapy, OS: overall survival, n: number of patients who underwent surgery. *Total recurrences; **more than 50% of the patients did not undergo axillary dissection; ‡approximately, of the entire cohort or from graphs.

Table IV. *Comparison of overall survival in male breast cancer (MBC) and female breast cancer (FBC).*

Author, year of publication (Ref)	n		Stratification	Overall survival		*p*-Value
	MBC	FBC		MBC	FBC	
Mc Donald *et al*. 2005 (21)	60	4181	Age, nodal status	5-Year: 75% 10-Year: 53%	5-Year: 82% 10-Year: 65%	0.11
Willsher *et al*. 1997 (14)	41	123	Age, grade and stage, time	5-Year: 55%	5-Year: 65%	0.27
Nilsson *et al*. 2011 (23)	99	396	No difference in stage between MBC and FBC	5-Year: 41%	5-Year: 55%	0.001
Müller *et al*. 2012 (27)	40	-	Virtual matching (Adjuvant!Online®)	5-Year: 66% 10-Year: 43%	10-Year: With comparable treatment: 59% With optimal treatment: 68%	<0.001
Ruschton *et al*. 2014 (32)	72	72	Age, time and stage	5-Year: 80%	5-Year: 80%	Not reported, (hazard ratio=1.345)
Yu *et al*. 2015 (39)	75	1313	Age, pT, SBR, margins, pN, treatment	5-Year: ~70%	5-Year: ~80%	0.009

SBR: Scarff-Bloom-Richardson grading.

postsurgical irradiation -without details concerning the volumes-although more than half presented a nodal invasion). A significantly worse prognosis was reported by McDonald *et al*. in males treated with radiotherapy compared to those without (21). Close margins were detailed in one study: Yu *et al*. demonstrated a trend in favor of radiotherapy for patients with close or unknown margins (25).

The study from the Surveillance, Epidemiology and End Results Program (SEER) database published by Abrams *et al*. in 2016, included 1933 patients in the entire cohort and 5-year overall survival was not significantly different between those receiving adjuvant radiotherapy and those not (78% *vs*. 77%, respectively, $p=0.371$). But in 315 cases in the same cohort, matched by ER status, T-stage, N-stage, race, histological grade and age, the use of adjuvant radiotherapy provided a benefit in 5-year overall survival (83% *versus* 54%, $p<0.001$). In patients with positive lymph nodes, for the entire unmatched cohort, the benefit of

radiotherapy achieved significance: 5-year overall survival was 79% *versus* 72%, $p=0.05$ in the group with one to three positive nodes, and 73% *versus* 53%, $p<0.001$ in the group with four and more positive nodes (18).

Studies comparing overall survival in MBC and FBC are additionally presented in Table IV.

Discussion

We achieved the gathering of data on 10.965 males over four decades, and this constitutes the largest review of the role of adjuvant irradiation for MBC. After mastectomy, radiotherapy improved local control in males with breast cancer according to available retrospective data reported in Table III, similarly as demonstrated prospectively for FBC (43). Radiotherapy also improved the overall survival, all the more so in men with positive lymph nodes. Our analysis reveals an inconstant use of radiotherapy after MBC and this finding raises some questions.

Important biases must be considered. The analysis is based on retrospective, often small, studies. The data were published over a long period which could lead to important variations in diagnosis and treatment modalities. For example, Cutuli *et al*. reported 5- and 10-year disease-specific survival rates of 74% and 51% in a first study (1960-1986) and 89% and 72% in a more recent survey (1990-2005) (12, 20). This improvement could be linked to better treatments or to earlier diagnosis. These studies report a reversal in the pattern of distribution between T1 and T2 in time: 20% of T1 and 41% of T2 in the first period compared to 47% of T1 and 20% of T2 in the second publication; T3-T4 stages accounted for about 30%. As described, the ratio of involved nodes did not change (53% and 56%), with approximately 20% of pN2 or more. But, even if T1 stages increased compared to T2 tumors, the rate of locally advanced MBC remained stable throughout the period. Improvement of the prognosis could therefore hardly be associated only with earlier diagnosis with modification of the stage distribution. Moreover, in the same period, the use of systemic treatments increased. As for radiation therapy, it is difficult to conclude that its use increased globally during this time because of the study's heterogeneity. However, studies from the large SEER American database showed a significant increase in the use of post-mastectomy radiotherapy over time (24.3% in 1973-1987 to 36.8% in 1998-2008, Fields *et al*. (6, 18).

MBC is often considered to be similar to post-menopausal FBC and treatment could, therefore, be based on the same recommendations. This assumption is questionable since important differences are emphasized in our analysis. MBC cases are mainly ductal since male breast lobules are not fully developed. MBC is rare before the age of 50 years and hormonal receptor positivity is more frequently reported. Nilsson *et al*. analyzed microarrays of 197 MBCs and found positivity for ER of 93%, PR of 77%, HER/2neu of 11%, with grade III (Nottingham) of 41%, luminal A of 81%, luminal B 11%, and rare basal-like phenotypes. This underlines a major gender difference since luminal A profile accounts for 44-66% of FBC, luminal B 6-19%, basal-like 10-17% and HER2-like 8-10% (44). Differences in genomic and molecular profiles between MBC and FBC suggest that these are different diseases (2, 23, 36, 45). Other significant differences in the immunostaining of MBC compared with FBC were also reported (46). A study published in 2016 showed, for instance, that a smaller percentage of MBCs compared to FBCs had mutation of phosphatidylinositol-4,5-*bis*phosphate 3-kinase catalytic subunit alpha (*PIK3CA*), this being the second most frequently mutated gene in FBC and the object of intense research for targeted therapies (47).

When considering the lack of screening with mammography, the predominance of T1 and T2 stages in most studies could be explained by the small breast volume in men, in which lesions are easily palpable. Moreover, delays in care are improving, perhaps due to increased public awareness (23, 48). However, nodal invasion remains at approximately 50% of MBC, with 20% or more of pN2, supporting the hypothesis of a higher risk of nodal invasion in MBC, even in those with small tumor size.

Comparisons between cohorts with matched MBC and FBC patients should then be considered with caution. Overall survival was often lower in MBC than in FBC even if not always significantly different. The comparison in outcomes according to gender is difficult as men were more likely undertreated, with less applied chemotherapy and less radiotherapy (25, 49). Men are additionally at higher risk of other cancer types and mortality causes (50). Older age at diagnosis results in higher comorbidities that could contribute to less access to therapies.

Considering adjuvant radiotherapy, in the absence of definitive data, it appears reasonable to support, at least, the use of the same recommendations as those available for FBC. After partial mastectomy, adjuvant radiotherapy appears mandatory. After radical mastectomy, chest wall irradiation is to be considered for men with involved nodes. In pN0. similar risk factors as in women (size, high grade, negativity for hormonal receptors, expression of *HER2neu*, lymphovascular invasion, dermal invasion) should be evaluated, but evidence is lacking. It is not possible to define precisely the target volumes such as the internal mammary nodes, a question that is still under debate for FBC. Data are also lacking in case of multifocality/multicentricity, and for inflammatory MBC. In the case of positive margins, one study showed a trend for a benefit with radiotherapy but we consider that positive margins should lead to repeat surgery as first intention and irradiation to the chest wall, possibly with a boost for residual disease if not resectable (25).

Some authors are in favor of a more aggressive treatment: Gennari *et al*., for example, proposed radiation therapy for tumors larger than 1 cm considering the small volume of the breast gland in males, especially since the male anatomy might facilitate early chest wall spread (51).

After MBC surgery, it is important to identify the situations where radiotherapy can be omitted in order to avoid exposure to unnecessary toxicity for the patient and unjustified costs. On the other hand, it remains important to emphasize the importance of adjuvant radiotherapy when indicated as our analysis reports its underuse in some cases, especially after partial mastectomy. Toxicity and impact on quality of life, which are potentially associated with adjuvant radiotherapy, could be considered as an issue for these patients who appear to be older and with more comorbidities than FBC patients. We consider that adjuvant irradiation can be proposed in safe conditions for these patients and that future evolution in radiotherapy will allow safer treatment modalities, even if new approaches have not been specifically evaluated in MBC. Hypofractionated regimens have not included men (neither in the English START trial nor the Canadian trial (52, 53). However modification of radiotherapy regimens due to age should be discussed in order to favor access to treatment when indicated. With dedicated computed tomographic scan planning, it is now possible to control the dose delivered to cardiac and pulmonary structures, especially in left-sided breast cancer, an important issue since male patients tend to have a higher incidence of coronary artery disease. The technique including internal mammary nodes in the tangential field appears to be of particular interest in this population (40, 54).

Despite the large number of cases collected in this review, it should be noted that arguments for radiotherapy in other prognostic subgroups than those with positive nodes, in which it is well supported, are not proven, but were also not excluded. It is, therefore, important to report real-life results from former series in order to assess the security of current practice. Large prospective cohort studies should be instigated for MBC. Such studies are difficult to conduct considering the epidemiology of MBC and the minor economic issues. At the same time, collaborative approaches should better characterize MBC with clinical and biological data, as proposed in the project "Male Breat Cancer: Understanding the Biology for Improved Care" initiated in 2010 and sponsored by the European Organisation for Research and Treatment of Cancer (NCT01101425).

Conflicts of Interest

The Authors have no actual or potential conflicts of interest including any financial, personal or other relationships with people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

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