# Radiation Therapy in Male Breast Cancer

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## Abstract

Male breast cancer (MBC) is a relatively rare disease and because the dedicated literature on MBC is limited, management typically follows guidelines established for female breast cancer (FBC). Although radiation therapy (RT) constitutes a critical role in the treatment of MBC, several unique challenges influence its use. Most men with breast cancer present at an older age with more extensive and advanced stage disease than women. In contrast to the predominance of breast conservation therapy in women with breast cancer, the majority of men are treated with mastectomy, with or without post-mastectomy radiation. Although no prospective or randomized trials are available, retrospective data suggests that surgery followed by adjuvant RT significantly improves locoregional control (LRC) in men. This article reviews the utilisation, efficacy, and complications associated with adjuvant RT in MBC.

## Keywords

Male breast cancer, radiotherapy, adjuvant, outcomes, locoregional control, survival

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In the US, approximately 1 % of all breast cancer cases and less than 1 % of all male cancers are male breast cancer (MBC) cases. An estimated 2,240 cases of MBC will be diagnosed in the US in 2013 compared with 232,340 cases of female breast cancer (FBC).[1] Due to its rarity, large prospective studies and randomized controlled trials focused on treatment options for MBC are not available. Management, therefore, has been largely dependent on results from large trials in women with breast cancer. Several unique challenges exist in men with breast cancer that influence the role of adjuvant radiotherapy (RT). Men are not screened for breast cancer and commonly present at an older age and higher stage than women, and are more likely to present with a palpable mass that is centrally located.[2,3] Due to the location and the low volume of normal breast tissue in men, there is a high propensity for nipple, chest wall, and nodal involvement[3,4] resulting in more advanced stage at diagnosis and possibly greater need for post-mastectomy radiation (PMRT).[2] Based on data from randomized clinical trials, adjuvant RT improves locoregional control (LRC) following lumpectomy and radiation in many circumstances.[5–8] In this article, we review the literature associated with the role of adjuvant RT in MBC.

## Role of Radiation Therapy in Locoregional Control

### Post-mastectomy Radiotherapy

In the US, PMRT has traditionally been indicated in women with four or more positive lymph nodes, T3 tumours, or stage III disease.[9,10] Multiple randomized trials have demonstrated improvement in LRC and overall survival (OS) with the addition of PMRT (see *Table 1*). The Danish 82b trial demonstrated the use of PMRT, in conjunction with systemic chemotherapy, reduced local failure (LF) by 23 % and improved disease-free survival (DFS) and OS by 14 % and 9 %, respectively.[7] In the Danish 82c trial the use of PMRT, in addition to hormonal therapy, reduced LF by 27 % and improved OS by 9 %.[8] The British Columbia trial similarly demonstrated a reduction in LF of 16 % with an OS improvement of 10 % with the addition of PMRT to adjuvant chemotherapy.[11]

For women with one to three positive nodes, the indications for PMRT are more controversial. A subgroup analysis of the Danish 82b and 82c trials included only patients with eight or more nodes removed, demonstrating that PMRT improved 15-year survival in all patients, and reduced LF rates in both groups of women with one to three positive nodes and four or more positive nodes.[12] The presence of high-risk features including young age, nodal ratio (number of positive nodes compared with number of nodes examined), lymphovascular invasion, extracapsular extension, margin status, and histological grade[13] also influence physician recommendations for PMRT. The standard treatment for PMRT is currently 30 treatments to the chest wall, level I–III axillary nodes, supraclavicular nodes and, in certain cases, internal mammary nodes, delivered 5 days per week. Hypofractionated regimens, or shorter treatment courses with larger doses of RT per treatment, are not commonly offered post-mastectomy due to limited data.

### Breast Conservation Therapy

Breast conservation therapy (BCT) is defined as partial mastectomy (e.g. lumpectomy, segmentectomy, quandrectomy) followed by RT with

**Table 1: Randomized Controlled Trials of Post-mastectomy Radiotherapy in Female Breast Cancer**

| Trial | Number of Patients | Patient Characteristics | Treatment Arms | Locoregional Recurrence | Survival |
|---|---|---|---|---|---|
| Danish 82b[7] | 1,708 | MRM<br>7.9 % N0<br>62.1 % N1–3<br>29.9 % N>3 | Adjuvant CMF<br>Adjuvant CMF + RT | CMF: 32 %<br>CMF + RT: 9 % | 10-year DFS<br>CMF: 34 %<br>CMF + RT: 48 %<br>10-year OS<br>CMF: 45 %<br>CMF + RT: 54 % |
| Danish 82c[8] | 1,406 | MRM<br>10 % N0<br>58 % N1–3<br>33 % N>3 | Adjuvant tamoxifen<br>Adjuvant tamoxifen + RT | T: 35 %<br>T + RT: 8 % | 10-year DFS<br>T: 24 %<br>T + RT: 36 %<br>10-year OS<br>T: 36 %<br>T + RT: 45 % |
| British Columbia[11] | 318 | MRM<br>57.5 % N1–3<br>35.2 % N>3 | Adjuvant CMF<br>Adjuvant CMF + RT | CMF: 28 %<br>CMF + RT: 10 % | 20-year BCSS<br>CMF: 38 %<br>CMF + RT: 53 %<br>20-year OS<br>CMF: 37 %<br>CMF + RT: 47 % |

*BCSS = breast cancer specific survival; CMF = cyclophosphamide, methotrexate, fluorouracil; DFS = disease-free survival; MRM = modified radical mastectomy; RT = radiation therapy; OS = overall survival.*

or without adjuvant hormonal or systemic chemotherapy. Since the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial demonstrated equivalent survival outcomes among women with breast cancer undergoing radical mastectomy, total mastectomy with PMRT, or simple mastectomy with axillary node dissection (ALND), there has been a shift to less extensive surgery.[6] NSABP B-06 compared modified radical mastectomy (MRM), lumpectomy, and lumpectomy with adjuvant RT, demonstrating that the addition of RT to lumpectomy reduced ipsilateral recurrence from 39.2 % to 14.3 %.[5] Similar results have been demonstrated for women with ductal carcinoma *in situ* (DCIS) in the European Organisation for Research and Treatment of Cancer (EORTC) 10853[14] and United Kingdom Coordinating Committee On Cancer Research trials.[15] The NSABP B-17 and B-24 randomized trials reinforced the results of B-06, with reduction in ipsilateral invasive and non-invasive recurrences with the addition of RT to lumpectomy.[16–18] The accepted fractionation for adjuvant RT after lumpectomy usually involves 30–33 treatments, delivered 5 days per week. Hypofractionated whole-breast RT delivered in 16–20 treatments has proved its safety in randomized trials[19–21] and is gaining acceptance in the US.

### Axillary Radiation

Currently, the primary indication for adding dedicated axillary RT in FBC is four or more positive lymph nodes following ALND or inadequate ALND.[22] The decision to add a field for supraclavicular nodal RT in patients with one to three positive nodes depends on other high-risk features (e.g. lymphovascular invasion, extracapsular extension, etc.) Regional nodal RT in women with more than four positive lymph nodes results in improved regional, axillary, and supraclavicular LRC.[23] The percentage of involved nodes is also predictive of axillary control rates, with improved rates when the percentage of involved nodes is less than, or equal to, 50 %.[24] This topic remains an area of investigational interest.

## Role of Radiation Therapy in Overall Survival

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis published in 2005[25] is an important study showing a survival benefit with adjuvant RT in FBC. Although none of the included breast cancer-specific trials independently demonstrated a survival advantage, this meta-analysis found a 5.3 % improvement in OS with the addition of adjuvant RT to partial mastectomy. In patients who were node positive, PMRT improved OS by 4.4 %. Adjuvant RT did not demonstrate a survival benefit in node-negative patients. Importantly, the survival benefit was only shown after 15-year follow up with thousands of patients, suggesting that subtle differences in survival may not be detectable in small trials with a short follow up. The EBCTCG analysis concluded that for every four recurrences prevented with adjuvant RT, one breast cancer death was avoided.[25]

## Radiation Therapy in Male Breast Cancer

The management of MBC has evolved considerably over the past several decades. Similar to the B-04 trial in women,[6] several studies found equivalent rates of LRC and OS with MRM and PMRT compared to radical mastectomy in MBC.[26,27] Furthermore, after sentinel lymph node biopsy (SLNB) became the gold standard tool for investigating nodal status in node-negative women,[28–30] studies have demonstrated oncological equivalency between ALND and SLNB in men.[31] More recent evidence suggests that BCT may even be an acceptable option for men with breast cancer, producing similar outcomes to mastectomy.[32] Many of the shifts in treatment paradigms would not be possible without the addition of adjuvant RT to surgery. We review the retrospective evidence for adjuvant RT in MBC (see *Table 2*) and note that, controlled for stage, RT results in similar outcomes compared with those in FBC.[33]

Retrospective series of men with breast cancer undergoing adjuvant RT demonstrate reductions in LF, ranging from 12 to 88 % (see *Table 3*). As early as the 1980s, a retrospective analysis of 89 men (81.4 % T1–2 and 55.9 % N1) receiving adjuvant RT showed improvements in LRC between 28 % to 55 %.[34] A series from Ireland published in 1984 showed that men who underwent PMRT had longer mean time to LF (mean 2.9 years compared with 1.8 years).[35] In 1990, a review of 16 patients demonstrated no LF in patients who received adjuvant RT, but a 66.7 % LF rate in patients after

## Table 2: Retrospective Series of Radiation Therapy in Male Breast Cancer

| Author(s)/Year | Number of Patients | Stage | Adjuvant Radiation Therapy | Radiation Dose and Treatment Volumes | Outcomes |
|---|---|---|---|---|---|
| Scheike 1974[50] | 257 | I–IV | 77 % | | 5-year OS: 46 %<br>10-year OS: 29 % |
| Ribeiro 1977[27] | 200 | I–III | N/A | Pre-1950 radium mold /needle implant<br>Post-1950 orthovoltage 250–300 kV | 5-year OS: 42.6 %<br>10-year OS: 26 % |
| Ramantanis et al. 1980[51] | 138 | I–IV | 15.9 % | | 5-year OS: 32.5 % (N- 56.5 %, N+ 30.8 %)<br>10-year OS: 14.8 % |
| Erlichman et al. 1984[34] | 89 | I–IV | 68.5 % | | 5-year N- OS: 77 %<br>5-year N+ OS: 37 %<br>5-year DFS: 45 % |
| Ribeiro 1985[26] | 292 | I–IV | 44.5 % | | 5-year OS: 52 %<br>10-year OS: 36 % |
| Spence et al. 1985[35] | 81 | I–IV | 81.5 % | Chest wall + ipsilateral axillary nodes: mean 4,135 rads | 5-year OS: 38 %<br>10-year OS: 17 % |
| Hultborn et al. 1987[52] | 166 | I–III | 78 % | | 5-year OS: 56.4 %<br>10-year OS: 32.9 % |
| Chung et al. 1990[36] | 16 | I–IV | 62.5 % | Chest wall, axilla, supraclavicular fossa, internal mammary nodes: range 46–64 Gy | 5-year OS: 57 %<br>10-year OS: 28 % |
| Guinee et al. 1993[53] | 335 | T1–4<br>N1–3 | 79.5 % | | 5-year N- DFS: 90 %<br>5-year N+ DFS: 65 % |
| Stierer et al. 1995[54] | 169 | I–IV | 38 % | | 5-year OS: 62 %<br>5-year DFS: 55 % |
| Cutuli et al. 1995[4] | 397 | T0–4<br>N1–3<br>M0 | 66.2 % | Chest wall: minimum 40 Gy | 5-year OS: 65 %<br>5-year BCSS: 74 %<br>10-year OS: 38 %<br>10-year BCSS: 51 % |
| McLachlan et al. 1996[55] | 66 | 0–IV | 34.8 % | Median 40 Gy/16 fx | 5-year OS: 63 %<br>Range 40–50 Gy/15–25 fx<br>Scar boost 8–12.5 Gy/4–5 fx |
| Schuchardt et al. | 21 | I–IV | 81 % | Median 50 Gy/25 fx<br>Range 32–60 Gy/16–30 fx | 5-year OS: 59 %<br>5-year N- OS: 67 %<br>5-year N+ OS: 56 %<br>10-year OS: 46 % |
| Willsher et al. 1997[38] | 43 | | 25 % | | 5-year OS: 55 % |
| Yildirim and Berberoglu 1998[45] | 121 | I–IV | 48.7 % | | 5-year OS: 50 % |
| Donegan et al. 1998[44] | 217 | 0–IV | 41.9 % | | 5-year OS: 50.6 %<br>10-year OS: 23.7 % |
| Stranzl et al. 1999[41] | 31 | 0–III | 100 % | Chest wall: range 40–50 Gy/20–25 fx<br>T4 tumours: boost 10 Gy/5 fx<br>N+ tumours: mean 46 Gy (range 40–50 Gy)<br>No ALND: mean 45 Gy | 5-year OS: 77 %<br>5-year DFS: 73 % |
| Goss et al. 1999[56] | 229 | 0–IV | 57.2 % | | 5-year OS: 53 %<br>5-year DFS: 47 % |
| Chakravarthy and Kim 2002[57] | 44 | I–III | 29.5 % | Chest wall and regional nodes: median 50 Gy, range 45–65 Gy | 5-year OS: 75 %<br>5-year DFS: 70 % |
| Atahan et al., 2006[43] | 42 | I–III | 100 % | Chest wall and lymphatics: median 50 Gy/25 fx, range 46–60 Gy/23–30 fx | 5-year OS: 77 %<br>5-year DFS: 45 % |
| Cutuli et al. 2010[37] | 489 | I–III | 85.3 % | Chest wall, supraclavicular fossa, axilla, internal mammary nodes: range 46–50 Gy | 5-year OS: 81 %<br>5-year BCSS: 89 % |
| Liukkonen et al. 2010[58] | 58<br>N± | T1–4 | 60 % | Chest wall or breast ± axillary and regional nodes | 5-year OS: 75 % |
| Bratman et al. 2012[42] | 22 | I–IV | 100 % | Chest wall and supraclavicular fossa: median 50.4 Gy, range 45–55 Gy/22–28 fx. Lumpectomy boost: 10–14 Gy. APBI: mean 38.5 Gy/10 fx | 5-year OS : 60 % |
| Yu et al. 2012[39] | 81 | I–IV | 56.8 % | Chest wall ± supraclavicular, axillary, or internal mammary: range 40–50 Gy/15–25 fx<br>Positive margin: boost 10 Gy/5 fx | 5-year OS: 73.9 %<br>10-year OS: 30 % surgery, 45 % RT<br>10-year LRC: 50 % surgery, 95 % RT |

*ALND = axillary node dissection; APBI = accelerated partial breast irradiation; BCSS = breast cancer specific survival; DFS = disease-free survival; fx = fractions; Gy = Gray; kV = kilovoltage; LRC = locoregional control; OS = overall survival; RT = radiation therapy.*

**Table 3: Impact of Radiation Therapy on Local Recurrence Rates in Male Breast Cancer**

| Author | Number of Patients | Patient Characteristics | 5-year Locoregional Recurrence | |
|---|---|---|---|---|
| | | | Surgery Alone | Surgery + Radiation |
| Erlichman et al. 1984[34] | 89 | Stage I–IV, 59 % N+ | 77 % | 45 % |
| Chung et al. 1990[36] | 16 | Stage I–IV, 46.2 % N+ | 66.7 % | 0 % |
| Cutuli et al. 1995[4] | 397 | Stage I–III, 56 % N+ | 14.2 % | 6.3 % |
| Schuchardt et al. 1996[40] | 21 | Stage I–IV, 66.7 % N+ | 100 % | 11.8 % |
| Willsher et al. 1997[38] | 43 | Stage I–IV, 24 % N+ | 27 % | 10 % |
| Chakravarthy and Kim 2002[57] | 44 | N 1–3+ | 6.5 % | 0 % |
| | | N >4 + | 3.2 % | 38 % |
| Yu et al. 2012[39] | 81 | All patients | 24 % | 4 % |
| | | High risk (stage III, N+, <2 mm margin) | 17.1 % | 0 % |

surgery alone.[36] A large series from Milan showed significant reductions in LF, as low as 1.6 %, with PMRT and nodal radiation.[37] A matched comparison of MBC and FBC patients demonstrated a dramatic reduction of ipsilateral axillary node recurrence, from 47 % to 20 %, with the addition of adjuvant RT.[38] An analysis of high-risk patients with positive nodes, stage III disease, and unknown or <2 mm resection margins, showed a reduction in LR rates with the addition of PMRT from 17 % to 0 %, and in all patients a reduction from 24 % to 4 %.[39] In a German cohort, all patients with surgery alone suffered a LF compared with only 11.8 % with the use of adjuvant RT.[40] In addition, an Austrian cohort of 31 men with stage I–III disease treated with adjuvant RT showed only a 3.2 % LF rate.[41] Data from Stanford also shows excellent control rates, with no isolated LF at 23 months in 22 men treated with adjuvant RT from 1960 to 2011.[42] Despite strong associations between PMRT and LRC, there remains a lack of evidence demonstrating survival benefit in men.[34,39,43–45]

There are no published guidelines for the use of adjuvant RT in MBC, but a few articles have outlined specific recommendations. A study from the UK encourages adjuvant RT for men with T3 tumours or T1–2 tumours with high-risk features, such as positive nodes, stage III disease, and unknown or <2 mm resection margins.[38] PMRT is also considered in cases of younger patient age, positive or close margins, positive nodes, high grade, large primary tumour size, involvement of the skin, areola, chest wall or pectoralis muscle, lymphovascular invasion, extracapsular extension, or multifocal disease.[13] Chung et al. advise including the ipsilateral internal mammary nodes, supraclavicular, and infraclavicular nodes in addition to the chest wall based on the fact that most tumours in men are centrally located.[36] Veronesi et al.[46] showed that internal mammary node involvement is more common in women with inner quadrant tumours, positive axillary nodes, and large tumour size. Many of these characteristics are common in MBC and therefore inclusion of the internal mammary nodes could be considered in PMRT for certain patients.

## Complications

Common acute complications after RT include fatigue, skin erythema, and desquamation. Rare, but serious, long-term complications include contracture of a reconstructed breast, telangiectasia, skin fibrosis, cardiomyopathy, pulmonary toxicity including radiation pneumonitis, lymphedema especially in patients who have undergone ALND, brachial plexopathy, costochondritis, rib fractures, and radiation-induced malignancies.[13,47] There is limited literature available on complications of RT in MBC. An Austrian review of men who received adjuvant RT reported no cases of a second malignancy in the irradiated field, a maximum of grade II skin toxicity scored by the Radiation Therapy Oncology Group (RTOG)/EORTC grading system and no severe late complications.[41] Bratman et al.[42] reported low toxicity rates with grade 1–2 dermatitis and fatigue, and Schuchardt et al.[40] reported similar acute and late toxicity with a maximum of grade II dermatitis.

## Emerging Concepts

### Breast Conservation Therapy in Male Breast Cancer

Although the majority of women with breast cancer are now treated with BCT, there has been a slower adoption in MBC. The majority of male patients are still treated with mastectomy. A recent Surveillance Epidemiology and End Results (SEER) analysis by Cloyd et al.[32] was the largest report of MBC patients treated with lumpectomy to date. This retrospective review demonstrated that, despite significant differences between patients who received lumpectomy versus those who received mastectomy, the type of surgery did not affect breast cancer specific survival or OS. Interestingly, only 35 % of BCS patients underwent adjuvant RT, significantly less than women undergoing BCS, and only 21 % of mastectomy patients received PMRT,[32] suggesting that adjuvant RT is possibly underutilized in men. Lumpectomy with adjuvant whole breast RT in select situations may be an acceptable option for men with early breast cancer.

### Hypofractionation

The standard treatment for adjuvant RT is a 6-week daily treatment course, and the efficacy of shorter course RT has been investigated. A trial from Canada compared standard fractionation (50 Gray [Gy] in 25 fractions) to a hypofractionated regimen (42.5 Gy in 16 fractions) and showed no difference in LRC, DFS, or OS in women who underwent lumpectomy.[21] The UK trials Standardisation of Breast Radiotherapy (START) A and B compared standard fractionation (50 Gy in 25 fractions) to hypofractionated regimens (39 or 42.6 Gy in 13 fractions and 40 Gy in 15 fractions, respectively) in women undergoing mastectomy (15 % in START A; 8 % START B) and lumpectomy.[19,20] Both trials demonstrated equivalent LRC and lower patient-reported toxicity rates in the hypofractionated arms. Trials examining hypofractionated regimens are ongoing, although the majority exclude men with breast cancer.[48]

### Accelerated Partial Breast Irradiation

Accelerated partial breast irradiation (APBI) is RT delivered to the lumpectomy cavity alone in a 10-day treatment course, allowing for a shorter course of treatment and decreased dose to the contralateral breast, heart, and lungs. In the US, APBI is considered in women if the lumpectomy cavity to whole breast tissue ratio is less than or equal to 30 %,[13] along with other pathological features that help guide

recommendations.[49] Men, having a smaller volume of breast tissue overall, are less likely to meet criteria for this treatment. A recently closed trial randomized women to either whole breast RT in 25–30 treatments or APBI in a 5-day, 10-treatment course,[48] and men were excluded. Nevertheless, APBI has been reported in MBC in certain situations.[42]

## Conclusions

Due to its relative rarity, management of MBC typically follows that of FBC. Randomized controlled trials in women overwhelmingly support the use of adjuvant RT to maintain LRC, and to a lesser extent, OS. The retrospective data presented in this review suggests that adjuvant RT in MBC provides a LRC benefit,[34–37,40–43] as has been shown in women. Survival data in men are limited due to the small numbers and lack of long-term follow up. New data suggest that MBC patients may safely undergo lumpectomy followed by adjuvant whole-breast RT. Although caution is warranted in interpreting retrospective studies, these data corroborate proven findings in large female trials. Since similar trials of large cohorts of MBC patients are unlikely to be performed, the management of MBC should continue to follow guidelines of FBC and retrospective studies will continue to play a vital role in the analysis of outcomes for men with breast cancer. ■


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