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The role of ipsilateral breast radiotherapy in management of occult primary breast cancer presenting as axillary lymphadenopathy

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ARTICLE INFO

Article history:

Available online 12 June 2011

Keywords:

Occult primary
Breast cancer
Axillary metastases
Axillary adenopathy
Radiotherapy
MRI

ABSTRACT

Aim: To assess the role of ipsilateral breast radiotherapy (IBR) in women with occult primary breast cancer presenting with axillary metastases (OPBC).

Methods: Patients with axillary nodal metastases and histological diagnosis of breast cancer without palpable, mammographic or ultrasonographic evidence of a breast primary were identified from a prospectively maintained single institution database. Imaging, surgery, radiotherapy, recurrence and survival data were collected. Patients whose breast cancer primary was detected on MRI (but occult on clinical examination and other imaging) were excluded from the analyses of IBR and outcome, but were included in other exploratory analyses.

Results: Fifty-five patients were included between 1975 and 2009. Median follow up was 68 months. Twenty patients had breast magnetic resonance imaging (MRI) in addition to other imaging. A primary breast cancer was detected in 7 of these 20. 48/55 patients had no detectable breast primary. 35/48 patients (73%) were treated with radiotherapy to the conserved breast, and 13/48 (27%) with observation. Patients who had IBR had better 5 year local recurrence free survival (LRFS) (84% versus 34%, $p < 0.001$), and relapse free survival (RFS) (64% versus 34%, $p = 0.05$), but no difference in overall survival (OS) (84% versus 85%, $p = 0.2$). There was no difference in 5 year LRFS (80% versus 90%: $p = 0.3$) between patients who received radiation of 50 Gy in 25 fractions versus ≥ 60 Gy.

Conclusion: Patients with OPBC should be managed with IBR and breast conservation, or mastectomy. Our data suggest it is not necessary to irradiate the breast to more than 50 Gy in 25 fractions.

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1. Introduction

Breast cancer presenting as axillary adenopathy with clinically occult breast tumour was first described by Halsted in 1907.¹ Reported series suggest that 0.3–1% of early breast cancers present with axillary metastases in the absence of a

breast primary on clinical examination or mammography.^{2–4} Where mastectomy is performed in such patients, a primary breast cancer is found in 45–82% patients.^{3,5–9} However, where the breast primary is occult following breast MRI in addition to clinical examination, mammogram and ultrasound, the frequency of detection of breast primary in

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doi:10.1016/j.ejca.2011.05.010

mastectomy specimen is lower (20–33%).^{10,11} Where the ipsilateral breast is untreated following removal of involved axillary lymph nodes, clinical ipsilateral breast cancer develops in around 40% of patients,^{7,12–15} such that many guidelines and authors recommend local treatment of the ipsilateral breast in OPBC.^{16,17} However, not all guidelines are in concordance with this advice, with European guidelines published in 2003 recommending against radiotherapy and surgery when breast MRI is negative.¹⁸

Traditionally, in the setting of OPBC, the ipsilateral breast was treated with mastectomy. However, small retrospective series comparing mastectomy to breast irradiation reported no difference in local control or survival.^{3,12,19,20} Given the cosmetic advantage of breast conservation, IBR has become the treatment of choice.^{19–23}

Retrospective series infrequently describe breast radiotherapy dose and fractionation. One series¹⁹ reported use of an escalated dose schedule of 60 Gy in 30 fractions whilst two others reported use of a standard adjuvant dose of 50 Gy in 25 fractions.^{12,20,24} However, to our knowledge no series has compared outcome in patients treated using different dose and fractionation schedules.

In the past decade breast MRI has come into routine practice, and is now recommended where patients present with axillary metastases from an occult primary breast cancer.^{12,16,25–27} MRI has high sensitivity in detecting occult primary tumours in the breast, and may facilitate breast-conserving surgery.^{10–12,27–31}

This study updates a previously published series of 29 patients from the Royal Marsden Hospital,²¹ with the aim of confirming, in a larger series, that treating occult primary breast cancer with IBR is a safe alternative to mastectomy in terms of local control and survival. We add to the literature a comparison of outcomes in patients treated using two different IBR dose and fractionation schedules, a comparison of local therapy versus no treatment, and an assessment of whether or not the incorporation of breast MRI into investigations helps reduce loco-regional recurrence.

2. Method

2.1. Study population

Patients with axillary lymph node metastases and histological diagnosis compatible with a breast cancer primary without palpable, mammographic or ultrasonographic evidence of a primary breast cancer were identified from a prospectively maintained single institution data base (Royal Marsden Hospital, London, UK) between 1975 and 2009. Patients with metastatic or advanced loco-regional (Stage IIIC) disease, primary breast cancer incidentally detected on staging CT imaging, previous breast cancer, incomplete data, breast primary detected in ectopic breast tissue, or final histological diagnosis other than breast primary were excluded.

2.2. Study design

The Royal Marsden Hospital Committee for Clinical Research approved the study as a service evaluation.

The primary end-point (measured in patients with OPBC, excluding patients whose breast primary was detected by MRI) was the difference in 5 year LRFS between those who received IBR, and those who did not. RFS and OS were also compared. An exploratory analysis compared 5 year LRFS between those who received escalated dose IBR (60 Gy/30 fractions or 50 Gy/25 fractions with boost) and those who received standard dose IBR (50 Gy/25 fractions, or 40 Gy/15 fractions). Patients whose breast primary was detected by MRI were excluded from these analyses as it was anticipated that the different local treatment received would be confounding.

Further exploratory analyses were performed in patients with OPBC including patients whose breast primary was detected by MRI. 5 year LRFS, RFS and OS were compared between patients who had ipsilateral breast therapy (wide local excision and radiotherapy, ipsilateral mastectomy, or IBR), and those who had none; and were also compared in patients

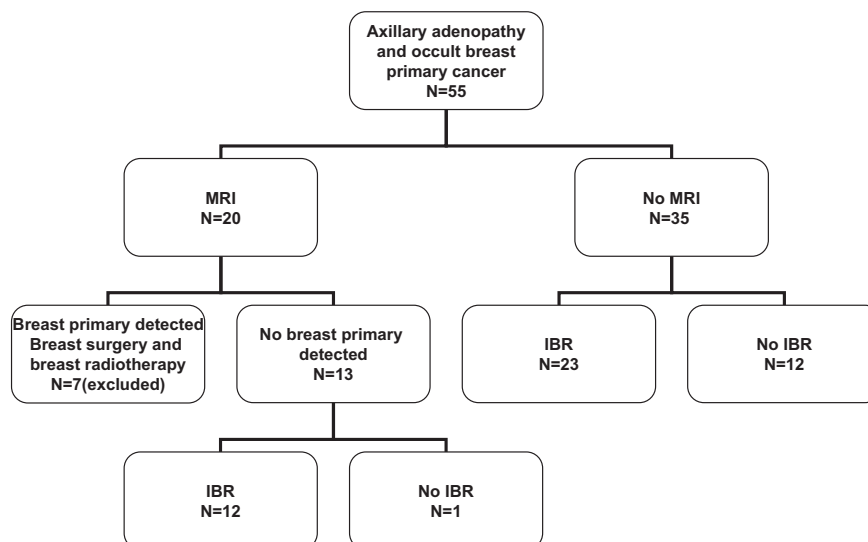


Fig. 1 – Diagrammatic representation of the groups of patients in the primary analysis, according to whether they had breast MRI and IBR.

who had ipsilateral breast therapy between those whose imaging included breast MRI, and those whose did not (Fig. 1).

2.3. Statistical analysis

LRFS is measured from diagnosis until the first isolated local recurrence and censored at last follow-up or at first distant metastasis. RFS is measured from diagnosis until a relapse in any site or death and is censored at last follow-up for pa-

tients who remain alive and disease free. OS is measured from diagnosis until death from any cause or last follow-up. All survival curves were calculated by the Kaplan-Meier method and differences were assessed by the log-rank test.

With a sample size of approximately 60, and three quarters of patients having breast radiotherapy, the study was predicted to have an 80% power to detect a difference in LRFS at 5 years of 95% in those who did receive breast radiotherapy compared to 30% in those that did not. Adjuvant chemotherapy and endocrine therapy were adjusted for using the Cox Proportional hazards model.

Table 1 – Patient characteristics and treatment received (patients with OPBC on all imaging including MRI).

Characteristic	Breast radiotherapy (N = 35)	No breast radiotherapy (N = 13)
<i>Age (years)</i>		
Median	57.5	45
Range	39–82	28–81
<i>Surgery</i>		
Axillary dissection	30 (86%)	9 (69%)
Involved node excised	5 (14%)	4 (31%)
Negative lumpectomy	2 (8%)	1 (8%)
<i>Oestrogen receptor</i>		
Positive	18 (51%)	8 (62%)
Negative	11 (31%)	1 (8%)
Unknown	6 (17%)	4 (31%)
<i>HER2 receptor</i>		
Positive	7 (20%)	0
Negative	9 (26%)	1 (8%)
Unknown	19 (54%)	12 (92%)
<i>Involved axillary nodes</i>		
pN0	1 (3%) ^a	0
pN1–3	16 (46%)	8 (62%)
pN > 3	18 (51%)	5 (38%)
<i>Adjuvant or neo-adjuvant chemotherapy</i>		
Yes	26 (74%)	6 (46%)
Anthracycline + Taxane ^b	7 (20%)	
Anthracycline ^c	16 (46%)	2 (15%)
CMF ^d	3 (9%)	4 ^e (31%)
No	9 (26%)	7 (54%)
<i>Adjuvant endocrine therapy</i>		
Yes	27 (77%)	7 (54%)
No	8 (23%)	6 (46%)
<i>Year of diagnosis</i>		
1975–2000	16 (46%)	12 (92%)
2001–2009	19 (54%)	1 (8%)

^a Negative axillary lymph node dissection after neoadjuvant chemotherapy.

^b Regimens used: adriamycin + cyclophosphamide (AC) × 4-paclitaxel × 4, EC × 4-paclitaxel × 4, epirubicin + cyclophosphamide (EC) × 4, accelerated paclitaxel × 4 (± herceptin), 5-fluorouracil + epirubicin + cyclophosphamide) FEC × 3-docetaxel × 3 (± herceptin). 2 patients received adjuvant herceptin.

^c Regimens used: epirubicin + cisplatin + 5-fluorouracil (ECF) × 4, FEC × 6, AC × 4.

^d Cyclophosphamide + methotrexate + 5-fluorouracil (CMF) × 6.

^e One patient received 6 cycles of cyclophosphamide + oncovin/5-fluorouracil + cyclophosphamide + oncovin + methotrexate (COF-COM) rather than CMF.

3. Results

3.1. Patient characteristics

Seventy-two patients were identified between 1975 and 2009, including 29 patients from the previously reported series.²¹ Seventeen patients were excluded for the following reasons: history of contralateral breast cancer (4), subsequent breast primary identified (1), non-breast histological diagnosis on review (1), incomplete data (1), breast primary arising in ectopic tissue (1), advanced breast cancer at diagnosis (7), and breast primary detected on staging CT (2). Therefore, 55 patients were included in the study. All patients had clinical examination and mammograms. Breast ultrasound scanning was performed in 30/55 (55%) and breast MRI in 20/55 (36%) patients. A breast primary tumour was detected by MRI in 7 of the 20 patients. 48 patients had no clinically or radiologically detectable primary breast cancer.

Median follow up was 68 months. Median age at diagnosis was 56 (range 28–82) years. Patient and disease characteristics for the 48 patients with OPBC compared in the primary endpoint are summarised in Table 1. Those for the seven patients whose breast primary was detected by MRI are summarised in Table 2.

3.2. Treatment

Of the forty-eight patients with OPBC, 35/48 (73%) received IBR, of whom 27/35 (77%) also had radiotherapy to the ipsilateral supraclavicular fossa (SCF), and 5/35 also to the ipsilateral axilla. 13/48 (27%) did not receive IBR. Of the 13 patients who did not receive IBR, 12 were treated before 2000, as local practise changed after that time. None of these 48 patients had mastectomy. 3/48 patients had partial breast excision surgery that did not reveal breast malignancy. 39/48 patients had axillary dissection surgery, and 9/48 patients had surgical excision of the involved axillary node only. More patients who had IBR had adjuvant chemotherapy and endocrine therapy, as described in Table 1. The treatment received by the seven patients whose breast primary was detected on MRI is described in Table 2.

3.3. Ipsilateral breast radiotherapy

Five of the 35 (14%) patients with OPBC who received IBR relapsed locally (2 in breast and 3 in loco-regional nodes) compared to 11 of 13 (85%) (10 in breast and 1 in loco-regional nodes) that had no IBR. The two patients that had IBR and

subsequently relapsed in the breast relapsed at 3.5 and 7.0 years, respectively, after diagnosis. Patients who had IBR had significantly better LRFS than those who did not (5 year LRFS 84% versus 34%, $p < 0.001$) (Fig. 2). RFS was also improved for those who had IBR (5 year RFS 64% compared to 34%; median 13 years 8 months compared to 2 years 3 months, $p = 0.05$) (Fig. 3). There was no difference in OS between the two groups (5 year OS 84% versus 85%, $p = 0.2$) (Fig. 4).

Given the difference in numbers, we adjusted for adjuvant chemotherapy and/or endocrine therapy using the Cox proportional hazards model. There remained no significant difference in OS between the group of patients who received IBR compared to those who did not ($p = 0.2$), and the effect of IBR remained significant for LRFS ($p < 0.001$), and for RFS ($p = 0.04$).

Table 2 – Patient characteristics and treatment received (patients in who a breast primary cancer was detected on MRI).

Characteristic	Patients (N = 7)
<i>Age (years)</i>	
Median	52
Range	38–71
<i>Surgery</i>	
Axillary dissection	7 (100%)
Involved node excised	0
Mastectomy	3 (43%)
Wide local excision	4 (57%)
<i>Oestrogen receptor</i>	
Positive	4 (57%)
Negative	1 (14%)
Unknown	2 (29%)
<i>HER2 receptor</i>	
Positive	3 (43%)
Negative	3 (43%)
Unknown	1 (14%)
<i>Involved axillary nodes</i>	
pN0	0
pN1–3	2 (29%)
pN > 3	5 (71%)
<i>Adjuvant or neo-adjuvant chemotherapy</i>	
Yes	7 (100%)
Anthracycline + Taxane ^a	4 (57%)
Anthracycline ^b	1 (14%)
Other ^c	2 (29%)
No	0
<i>Adjuvant endocrine therapy</i>	
Yes	4 (57%)
No	3 (43%)
<i>Radiotherapy</i>	
Chest wall or breast	7 (100%)
Ipsilateral SCF	6 (86%)
Axilla	0

^a Regimens used: AC × 4-paclitaxel × 4, FEC × 3-docetaxel × 3.

^b Regimens used: FEC × 6.

^c Regimens used: EC × 4-gemcitabine + carboplatin (GC) × 4, docetaxel × 4.

3.4. Patients whose breast primary cancer was detected by MRI

None of the seven patients had a local recurrence. One of the seven patients had distant relapse 1 year 2 months after diagnosis and died from breast cancer 2 years 7 months after diagnosis. Another had distant relapse at 2 year 7 months (31 months) and remains alive with disease. The other patients remain alive and free of breast cancer.

3.5. Breast radiotherapy fractionation and schedule

Information regarding breast radiotherapy fractionation and schedule was available for 31 of the 35 patients with OPBC who received IBR. 12/31 patients had escalated dose radiotherapy (either 60 Gy/30 fractions, or 50 Gy/25 fractions with 10 Gy boost), of whom 1/12 had a local relapse. 19/31 patients had standard radiotherapy (50 Gy/25 fractions, or 40 Gy/15 fractions), of which 3/19 relapsed locally. The dose and schedule used were according to individual clinician's preference. There was no significant difference in 5 year LRFS (90% versus 80%; $p = 0.3$) (Fig. 5), 5 year RFS (73% versus 62%, $p = 0.6$), or in 5 year OS (82% versus 94%; $p = 0.5$) between escalated and normal fractionation schedules. No difference was seen between those who had RT to the SCF (27/35) compared to those who did not (8/35) in 5 year LRFS (87% versus 83%, $p = 0.1$), 5 year RFS (69% versus 67%, $p = 0.1$) and 5 year OS (89% versus 80%, $p = 0.07$).

3.6. Ipsilateral breast treatment

Patients who had breast treatment (IBR or breast surgery and radiotherapy) had significantly better 5 year LRFS (87% versus 34%, $p < 0.001$) (Fig. 6) and better 5 year RFS (65% versus 34%, $p = 0.02$). No difference in 5 year OS was seen (83% versus 92%, $p = 0.1$).

3.7. MRI

Twenty patients had MRI incorporated into their breast imaging. In 7/20, the breast primary was detected, and they went on to have breast treatment (described in Table 2). 13/20 had OPBC. 12/13 of these patients received IBR, and one did not. 35 patients had no breast MRI. 23/35 received IBR, and 12/35 did not (demonstrated in Fig. 1). The 19/20 patients who had breast MRI followed by breast treatment were compared to the 23/35 patients who had breast treatment without having had an MRI, in an exploratory analysis. No significant difference in 5 year LRFS (90% versus 85%; $p = 0.6$), 5 year RFS (63% versus 69%; $p = 0.8$), or 5 year OS (90% versus 81%; $p = 0.8$) was seen between the two groups.

4. Discussion

The previously published series from our institution found that, in patients who presented with axillary lymphadenopathy from OPBC, breast conservation is a feasible alternative to mastectomy, but recommended that the ipsilateral breast be treated with radiotherapy to reduce local recurrence.²¹ These

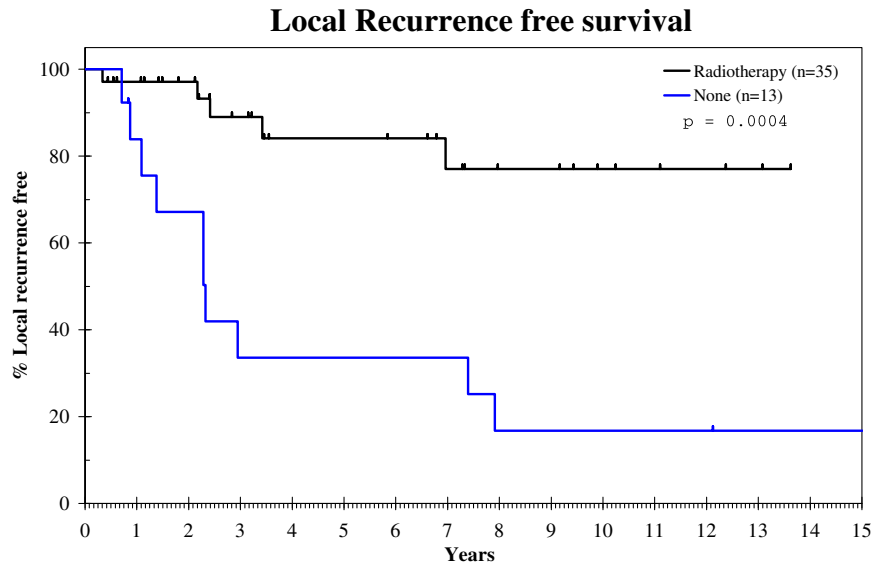


Fig. 2 – Local recurrence free survival according to whether the patient was treated with IBR.

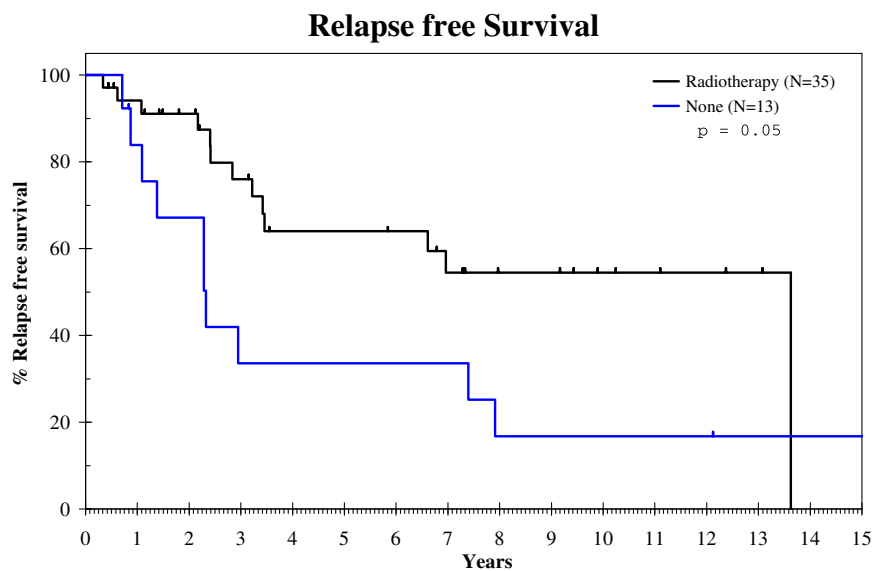


Fig. 3 – Relapse free survival according to whether the patient was treated with IBR.

updated results provide further support for this recommendation by showing that IBR significantly improves LRFS and RFS compared to breast observation.

Limitations of our study include its observational nature, the heterogeneity between patient groups, and the long period of accrual. The fact that only 1 of the 13 patients who did not receive IBR were treated before 2000 creates potential bias because a decline in breast cancer mortality³² and improvements in imaging modalities over this time period.²⁷ The introduction of ultrasound, digital mammography and routine breast MRI in the early 2000s may have created differences in the breast cancer characteristics and treatment received by patients. Although the effect of IBR is independent of adjuvant systemic therapy, an additional bias is

created by differences in adjuvant chemotherapy, favouring the group that received IBR (in which more received anthracycline-containing 2nd and 3rd generation chemotherapy regimens). Although more patients who received IBR had axillary dissection, axillary nodal burden is similar between the two groups, which is important given that number of involved axillary nodes is negatively prognostic.^{20,33}

Whilst acknowledging these limitations in the interpretation of our results, we believe our series provide one of the largest numbers of patients with the longest follow up to date in this rare clinical entity of occult primary breast cancer. Furthermore, our findings of a local recurrence rate (LRR) of 5/35(14%) in the group who received IBR, compared to 11/13(85%) in those who did not, are comparable to other

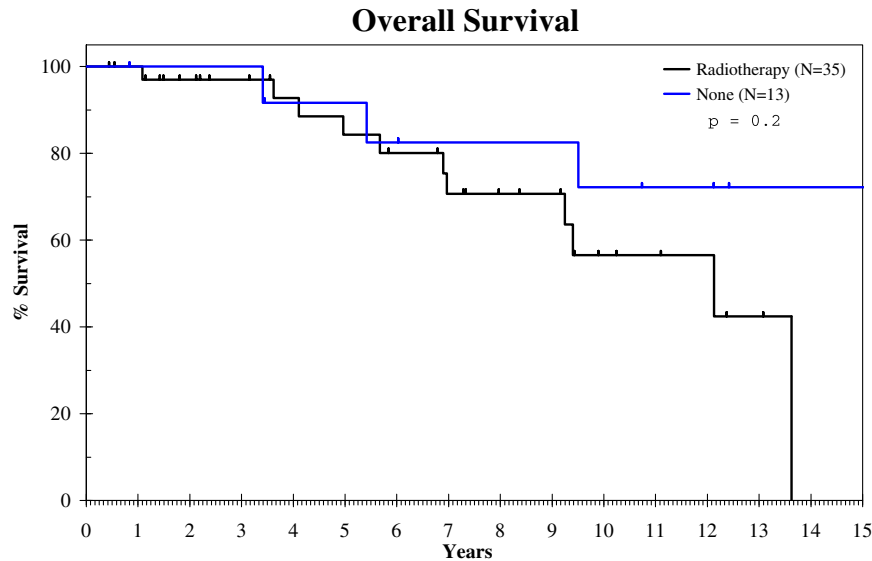


Fig. 4 – Overall survival according to whether the patient was treated with IBR.

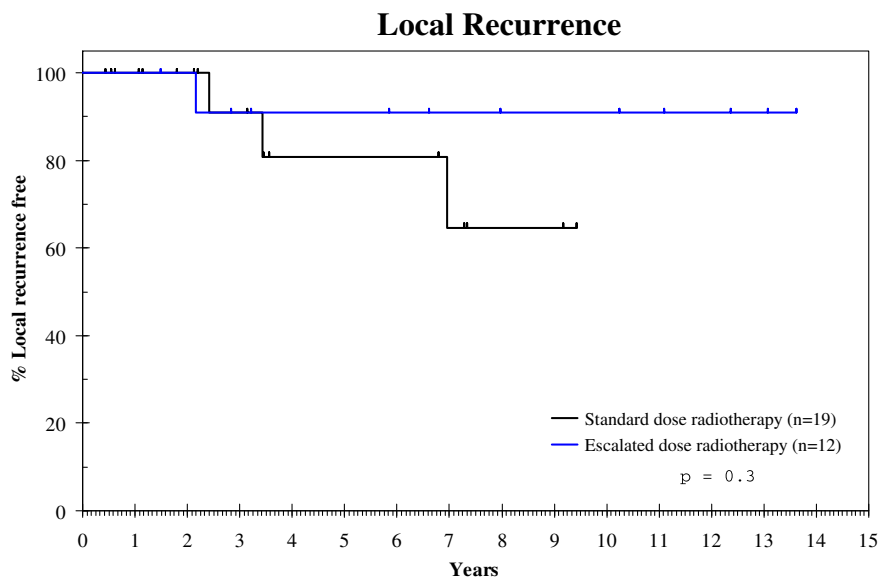


Fig. 5 – Local recurrence free survival according to whether the patient was treated with escalated/high dose radiotherapy to the ipsilateral breast (60/30 or 50/25 with boost), or standard dose (50/25 or 40/15).

published data. Series from the MD Anderson, Westmead hospital, Institute Curie, and the previous Royal Marsden series found a LRR of 12.5–36% in patient who received IBR compared to 54–83% in those who did not.^{12,19,21,24}

A recently reported series compared outcome following treatment of patients presenting with OPBC with either mastectomy or breast observation.⁹ 10/38 (26%) patients who had mastectomy had a local relapse compared to 10/13 (77%) who had breast observation. These data support the present clinical impression that mastectomy and breast conservation with radiotherapy achieve comparable clinical outcome.

The standard of care in terms of radiotherapy dose and fractionation is not well defined, and most of the literature predates the era of MRI. MRI is capable of detecting smaller

deposits of breast cancer (below the resolution of mammography and ultrasound).²⁷ It is thought that standard-dose breast radiotherapy (50 Gy/25 fractions or equivalent) is capable of sterilising such small volume disease.³⁴ Escalating dose beyond 50 Gy is unlikely to significantly improve local control of small volume disease but will significantly increase toxicity.³⁵ Consistent with this hypothesis, we found no significant difference in outcome between patients who received standard and escalated dose radiotherapy. Local recurrence was infrequent in both groups, suggesting that standard and escalated radiotherapy schedules in treatment of occult primary breast carcinoma are likely to be iso-effective.

We also investigated whether ipsilateral breast therapy significantly influenced prognosis. As anticipated, ipsilateral

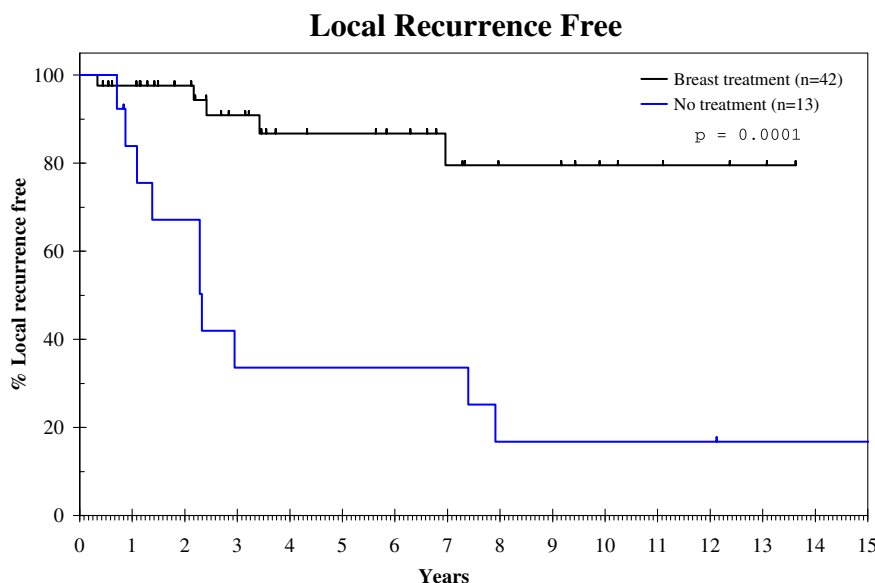


Fig. 6 – Local recurrence free survival according to whether the patient’s ipsilateral breast was treated (radiotherapy and/or surgery) or not.

breast therapy improved LRFS, consistent with other published literature.^{7,9,12,24,36}

Our rate of detection of breast primary cancer by MRI was slightly lower at 35% than in other reported series (36–86%).²⁷ The reason for this is unclear. One could speculate that our rate of detection of breast cancer primary on standard imaging was high. In patients who had ipsilateral breast treatment, we found no difference in outcome when breast MRI was performed in addition to routine imaging. However, this analysis was not sufficiently powered, and the fact that none of the seven patients whose breast tumour was detected with MRI relapsed locally following local breast and adjuvant treatment, would support the use of breast MRI.

5. Conclusion

Patients who have occult primary breast cancer with axillary metastases should be managed with local treatment of the ipsilateral breast. Where the ipsilateral breast is conserved, IBR is recommended to improve local control. No difference in outcome was found between patients treated with a standard breast radiotherapy fractionation and schedule (50 Gy/25 fractions or 40 Gy/15 fractions) and those treated 60 Gy/30 fractions.

Conflict of interest statement

None declared.

Acknowledgements

Sarah Barton would like to thank the Cridlan Fund for funding support. We acknowledge NHS funding to the NIHR Biomedical Research Centre.

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