The Breast 54 (2020) 211–215

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Review

Occult breast cancer: Where are we at?

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A R T I C L E I N F O

Article history:
Received 12 June 2020
Received in revised form
15 October 2020
Accepted 24 October 2020
Available online 27 October 2020

Keywords:
Occult breast cancer
pathological occult breast cancer, pOBC

A B S T R A C T

Occult breast cancer (OBC) is described as an axillary metastatic carcinoma without detection of a primary breast lesion and is uncommon. Significant advances in breast imaging have occurred since its description, decreasing its incidence. However current management is based upon old studies, with variable clinical, radiological and pathological definitions of OBC. We suggest standardised definitions of OBC to facilitate more homogenous data representation in the literature. This review also discusses the conflicting heterogeneous data and its influence in determining the current management guidelines. We discuss whether the current significant surgical recommendations are necessary and postulate whether they could be safely substituted with less invasive management.

Contents

Introduction . . . 211
Diagnostic techniques and their effect on the incidence and definition of OBC . . . 212
The impact of pathological techniques on OBC incidence . . . 212
Standardising definitions . . . 212
Management of OBC . . . 212
Chemotherapy in occult breast cancer . . . 214
Sentinel node biopsy in occult breast cancer post NAC . . . 214
Conclusion . . . 214
Funding source . . . 214
Ethical approval . . . 214
Declaration of competing interest . . . 214
References . . . 214

Introduction

The majority (98.9%) of cases of generalised lymphadenopathy are benign and most likely viral in origin [1]. Malignancy is diagnosed in 20% of those with persistent lymphadenopathy. Clinical axillary lymphadenopathy is common and yet there are no studies that specifically evaluate its aetiology. In greater than 50% of these latter cases, the primary originates from the breast [2–4].

Commonly a breast lesion is identified, but on occasion no primary is found. This is termed occult breast cancer (OBC) and was first described in 1907 as “cancerous axillary glands with non-demonstrable cancer of the mamma” [5]. Initially, OBC was defined by the absence of an in-breast clinical finding alone but the definition has broadened to also include negative mammography and ultrasonography. The incidence of the latter is reported as being 0.3–1% of all breast cancer patients [6–8]. The incidence of the latter is 0.1–3%. It is thought that OBC is secondary to micro-invasive breast cancer [9].

The introduction of better diagnostic techniques and more detailed pathology continue to impact the true incidence of OBC,

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https://doi.org/10.1016/j.breast.2020.10.012

yet national guidelines surrounding its management have not changed and are based upon studies that have varying definitions of OBC dependent on the level of technology used at the time [10].

This review aims to discuss the changes in the diagnosis and subsequent management of OBC.

Diagnostic techniques and their effect on the incidence and definition of OBC

The American College of Radiology recommends the use of MRI for OBC patients that do not have evidence of a breast primary on traditional radiological examination (mammogram and ultrasound) and clinical exam [11]. Level I evidence has shown MRI is significantly more sensitive in detecting a primary lesion that mammography or ultrasound; identifying a primary in 72% of cases that were deemed occult [12]. Currently, 3.0 T (T) breast MRIs have demonstrated greater spatial resolution and improved signal to noise ratio, compared to earlier 1–1.5T MRIs [13,14]. This has resulted in improved detection and a better positive predictive value [15].

Other imaging techniques have been reviewed as an alternative to MRI, to improve the detection of occult primaries. In a comparative analysis to MRI in 2015, Contrast enhanced mammography (CEM) had equivalent if not better sensitivity (100% vs 93%) than MRI in detecting breast cancers [16]. Further papers have supported this finding, however CEM has yet to be evaluated specifically in the setting of OBC [17,18].

Diffusion-weighted (DW) MRI (where water molecule mobility is decreased in the cancer microenvironment and contrast is not required) may be an adjunct to existing MRI techniques [19]. DW-MRI may be useful in the future in increasing detection rates, however it still requires further standardisation to ascertain its true sensitivity and specificity [20].

Fluorodeoxyglucose (FDG)-positron emission tomography (FDG PET/CT) has been used in occult breast cancer, however there is only one case report in the literature to date, in which FDG PET/CT has detected a primary breast tumour over MRI [20]. Positron emission mammography (PEM) is a newly emerging investigatory tool which uses FDG to localise smaller tumours especially those less than 1 cm and has a greater sensitivity than PET/CT in this subset of patients with small tumours [21]. A randomized multicentre study by Berg et al. (2011) compared PEM to MRI in 388 newly diagnosed breast cancer patients [22]. Though PEM had higher specificity (91.2% vs 86.3%), MRI showed greater sensitivity in detecting additional cancers (53% vs 41%). PEM is therefore not recommended over MRI at this time.

The impact of pathological techniques on OBC incidence

In addition to MRI and other imaging techniques, pathology can also affect the incidence of OBC. Buchanan et al. (2005) reported on 69 OBC patients (negative clinical exam, mammogram and ultrasound) who also underwent MRI [23]. Of the 55 patients; 13 had a negative-MRI (23.6%), of these 8 underwent mastectomy with a primary breast lesion found in 2 cases. Only 20% did not have a primary found after MRI and pathology were performed. Wang et al. (2010) reported on 51 patients who had OBC - defined as a negative clinical exam and mammogram and ultrasound [24]. Most of the group, 36 (71%) did not undergo MRI. Of the 51 patients, 38 came to mastectomy. Cancers were detected in 6 (15.8%) of these patients with “routine pathology”. When slide intervals were reduced to 5 mm, a further 22 (57%) cancers were found; detailed pathology therefore detected lesions in 74% of cases.

Standardising definitions

Much of the OBC literature upon which determines current guidelines, is based upon heterogeneous cohorts from population databases or institutions that include patients who may or may not have had MRI and who may not have had detailed breast pathology performed. As the sensitivity of any diagnostics improves, the incidence of OBC decreases and the definition of OBC must alter accordingly so that we can make better evidence-based management decisions about particular subsets of patients.

For the purposes of this discussion and to assist in clarifying the available data, we use two separate OBC terms. Clinical occult breast cancer (cOBC) is defined as no lesion detectable on examination, mammography and ultrasound and pathological occult breast cancer (pOBC) which extends beyond cOBC, includes a negative MRI and, if performed, a pathologically negative mastectomy specimen (when examined at 5 mm slices).

Management of OBC

Node positive (N1) OBC patients have been reported to have a better overall survival (OS) rate to matched patients with T1N1 disease [25,26]. If this is true, then theoretically it may be possible to take a more minimalistic approach to management. To date, standard practice for patients with cOBC is to perform an axillary lymph node dissection (ALND), but the optimal management of the ipsilateral breast in OBC has been controversial and varied.

In a study of 142 patients from multiple Korean institutions, observation of the ipsilateral breast in conjunction with ALND was compared to ALND and breast surgery whether by Mastectomy or breast conserving surgery (BCS) [26]. The study reported that there was no significant difference in OS between the groups. This suggested that no treatment was potentially necessary for the ipsilateral breast. However, at least 53% of the ALND alone group received radiation (RT) to the breast and it was unknown as to whether a further 25% received radiation or not. Therefore, this was not a homogeneous cohort. No subset analysis was performed of those that had truly received no treatment to the breast (which could have equated to only 25% of the cohort). In this study, data was collected over a 20-year period from 1990 onwards and it is not clear if any of the patients were pOBC or even if the study excluded patients from analysis who had cOBC with a positive MRI. This study demonstrates the difficulties interpreting the current literature when cohort definitions are so heterogeneous.

Wang et al. (2010) performed a retrospective review of 51 patients from a single institution with cOBC, of which 38 had ALND + Mastectomy and 13 patients had ALND only [24]. All patients had chemotherapy and those that were estrogen and progesterone receptor positive received hormonal therapy. These cohorts were therefore more homogenous than the Korean study. Thirty six of 51 patients underwent RT to the supraclavicular fossa. It was not clear as to whether all of the patients receiving RT were in the mastectomy arm, but it is assumed the majority were since the observation arm were patients who refused primary breast treatment inclusive of surgery ± RT. Fifteen of the 51 patients also had a negative MRI - it is also unclear as to which group these patients were in. In the mastectomy group there was a disproportionate number of patients with N1 disease (Table 1). In addition, after pathology of the breast was performed there were only 10 patients in the mastectomy group in whom a primary breast lesion could not be found.

Patients were followed for at least 4 years, with overall recurrence rates reported at 26% in the mastectomy group, compared to 77% for the ALND only group. Despite the cohorts not being matched (for either RT to the regional supraclavicular nodes, MRI or

Table 1
Mortality rates for ALND alone versus ALND + Mastectomy relative to nodal status [24].

	ALND alone		ALND + Mastectomy	
Nodal Stage	Total Cases	Deaths (%)	Total cases	Deaths (%)
I	6	2 (33)	23	2 (9)
II	3	2 (66)	7	1 (14)
III	4	4 (100)	8	4 (50)
	13	8 (62)	38	7 (18)

ALND, axillary lymph node dissection.

nodal status) the disease free survival (DFS) and OS rates were statistically far superior for mastectomy patients compared to observation alone - mean DFS of 76 vs 23 months ($p < 0.001$) and OS 82% versus 54% respectively ($p < 0.001$, mean follow up 73 months) [24]. One could conclude that surgery in the ipsilateral breast was of benefit when compared to no treatment. However, it is important to note that only 10 or less, of 38 patients, would fit our definition of pOBC.

A meta-analysis reported outcomes for OBC in patients undergoing ALND with either Mastectomy ± RT versus breast RT only [27]. This study also compared a second cohort undergoing ALND with either breast RT or no breast treatment. It included 7 international studies, with 241 patients presenting between 1973 and 2011. The mean follow-up was 62 months (SD 16.2 months). Patient cohorts were not matched for postoperative chemo-hormonal therapy. When comparing ALND + breast RT to ALND + Mastectomy ± RT, there was no statistically significant difference in loco-regional recurrence (LRR), distant metastases or mortality rates ($p = 0.78$, 0.16 and 0.65 respectively).

When reporting on the second comparison, ALND + breast RT to ALND alone, there was statistical evidence of a reduction in LRR ($p < 0.01$) in the radiation group but no statistical improvement when comparing distant metastases and mortality rates ($p = 0.17$ and 0.09 respectively). It was concluded that ALND + breast RT was better than ALND alone in terms of LRR; with only a trend towards lower distant metastases and mortality rates. While there was no direct comparison between the surgical and observational arms alone, it can be extrapolated that the outcomes would have been the same as there was no difference in the comparison between the surgery and radiation arms. This outcome is consistent to Wang et al.'s retrospective review.

MRI use was not uniform between the groups in terms of criteria for defining OBC; in fact, the only uniform criteria was a negative clinical exam, mammogram and ultrasound. Only 2 of 7 studies specifically excluded patients from the analysis if pathology confirmed disease post-operatively [6,28]. This resulted in a variable inclusion-criteria for patients with OBC across these studies.

A small study pioneering the use of radiation instead of surgery for the management of the ipsilateral breast was performed by The Institut Curie (1989) when they reported on 31 OBC patients who underwent radiotherapy to the ipsilateral breast, axilla and regional nodes (both supraclavicular and internal mammary chain) [29]. Two patients had RT as outlined alone, 29 patients had an additional axillary clearance. One patient had no breast radiation but mastectomy instead. The 5-year LRR for the whole group was reported as 13% and OS as 76%.

Subsequently two studies compared cOBC patients who received ipsilateral breast RT to those that did not. Ellerbroek et al. (1990) demonstrated a 40% reduction in LRR in the radiation group (n = 16, LRR 17%) versus the observation group (n = 13, LRR 57%) [30]. These results were reproducible in a similar sized cohort by Shannon et al. 10 years later [31]. They reported on 29 patients who had surgery to the axilla, 16 received RT to the ipsilateral breast ± chest wall and 13 had no RT to the breast. LRR rates were 12.5% versus 69% in favour of the RT arm ($p = 0.02$) with median follow up 44 months.

More recently, Masinghe et al. (2010) reported upon 53 patients who all had surgery to their axilla (biopsy, sampling or clearance) and either regional node RT (n = 12) or ipsilateral breast RT ± regional node RT (n = 41) [32]. LRR was 54% in those treated with regional node RX alone compared to 28% in those that had both regional nodes and breast radiation. In this study there was a mixture of cOBC and pOBC (n = 13) and subset analysis was not performed. Despite this, one can conclude that those that received treated to the breast did better. Kim et al. reported on 66 patients with pOBC who underwent ALND and whole breast radiation except for three [33]. Fifteen of the 66 patients had a blind upper-outer quadrantectomy with negative pathology. Univariate analysis at 8 years suggested a better DFS (89.5% versus 50%) and lower LRR (14% versus 67%) in the group receiving whole breast radiation than in the observation group (note n = 3).

These studies suggest that ALND with ipsilateral breast RT is, like surgery, superior to observation alone. Though these cohorts did not include pure subsets of pOBC, and had in some cases small sample sizes, the difference in LRR between the groups was quite sizable.

Pentheroudakis et al. (2010) published their systematic review of 24 OBC studies, which included 689 patients [34]. The majority of the patients were included if they had a negative mammogram and clinical exam (however 605 patients did not receive ultrasonography), 162 patients had an MRI and a lesion was identified in 96 (59%). Of the 446 patients who had mastectomy, 321 (72%) patients were found to have a lesion on pathology. Five-year OS ranged from 59.4 to 88% (mean 72%) over a 62-month period.

Walker et al. (2010) reviewed 750 OBC patients from the Surveillance, Epidemiology and End Results (SEER) database who underwent variable modalities of treatment between 1983 and 2006 [7]. Patient groups included observation alone (n = 94), ALND alone (n = 126), ALND + mastectomy ± RT (n = 268) and ALND + RT (n = 202). The majority of these patients however did not undergo MRI, and details pertaining to RT or systemic therapy were not reported. Ten-year OS was 47.5% in the observation group, 58.5% in the ALND only group and 64.9% in the ALND + ipsilateral breast treatment (mastectomy ± RT or radiation alone). Treatment of the breast was statistically superior to ALND alone and observation only ($p = 0.02$, $p = 0.04$ respectively). It did not seem to matter whether the breast was treated by radiation alone or by surgery as difference in OS between these two groups was not significant.

Wu et al. (2017), also retrospectively reviewed outcomes of ALND with either observation (n = 219) or ipsilateral breast treatment (n = 761) from the SEER database [35]. Breast treatment groups included surgery (BCS or mastectomy alone, n = 263), RT alone (n = 252), or surgery + RT (n = 246). When comparing ALND alone with all of the breast treatment options together, the 10-year cause specific survival rate and OS was significantly better in the ipsilateral breast treatment arm, 71.5–81% versus 57.2% ($p < 0.001$) and 67–69.5% v 46% ($p < 0.001$). There was no significant difference in OS between the three treatment arms. Additionally, ALND with either surgery or RT had equivalent outcomes. This study confirms the results in Macedo et al.'s meta-analysis that ALND with either surgery or RT is superior to ALND alone, and also suggests that there is no additional benefit to performing both surgery and RT to the ipsilateral breast ± chest wall. This is counterintuitive to recent non-occult breast cancer studies that suggest RT to the chest wall post mastectomy for N1 patients improves LRR [36–38].

Another recent study by Hessler et al., using the National Cancer Database (NCDB), reviewed management outcomes in 1231 patients with OBC [9]. When comparing 5-year OS across all 4 treatment groups, ALND and treatment of the ipsilateral breast regardless of the type of treatment was better than ALND alone or observation alone (Table 2). ALND with RT was superior to any other ipsilateral breast treatment (HR 0.48, $p = 0.001$) and was an independent significant variable on multivariable analysis [HR 0.51, $p = 0.004$].

The studies discussed above contained cOBC patients with a varied number having negative MRIs included in each study and even some including pathologically positive patients in analyses. The only review of pOBC patients comparing mastectomy to whole breast RT (WBRT) has been performed at Memorial Sloan Kettering Cancer Center (MSKCC) by McCartan et al. (2017) [39]. Thirty-eight patients were treated as per current National Comprehensive Cancer Network (NCCN) guidelines with either ALND and WBRT ($n = 25$) or ALND and mastectomy ($n = 13$). All patients had an MRI and all patients received chemotherapy. The only difference between the groups was that there was a greater number of patients who received radiation to the regional nodes in the radiation group (67%) versus the surgery group (46%). At a median follow up of 7 years, there was no local or regional recurrence in either arms. Ten-year DFS for the ALND and mastectomy group was 77%, compared to the ALND and WBRT group of 67%. Though sample size was too small to statistically compare DFS, confidence intervals were wide and overlapped, suggestive of no statistical significance. This would suggest that if that if there is pOBC then ALND + ipsilateral breast RT ± regional nodes is a reasonable option rather than a mastectomy. This study, as well as Wu et al. and Walker et al., all performed univariate and multivariate analysis to adjust for confounding variables.

Chemotherapy in occult breast cancer

Gene expression signatures in pathologically node-positive breast cancer patients is now an option in helping to guide decision regarding chemotherapy when it is less clear as to benefit [40]. Tissue for testing would need to be nodal in origin however and there is no data as to whether oncotype testing is accurate when using nodal tissue as opposed to breast tissue. This is a tool that needs further development before it can be used to guide the use of chemotherapy in patients with pOBC.

There is little additional evidence to guide the use of neoadjuvant chemotherapy either in patients with clinical and radiological OBC. Rueth et al. (2015) reviewed 36 patients defined as cOBC (33 of these had pOBC); 25 patients underwent neoadjuvant chemotherapy with an 80% pathological complete response (pCR) in the axilla [28]. The regimens discussed were 12 cycles of platinum, FAC/FEC for 4 cycles, with HER-2 treatment as appropriate. Patients underwent either ALND + mastectomy ($n = 9$), ALND + ipsilateral breast RT ($n = 24$), External beam radiotherapy (EBRT) to the ipsilateral breast and axilla ($n = 1$), EBRT to the breast only ($n = 1$) or endocrine therapy alone ($n = 1$). The 5 and 10-year DFS rates for the whole group were 100% and 97.2%. Subset analysis of the 25 patients receiving neoadjuvant chemotherapy was not reported on. The overall rate however is comparable to the Memorial study which included patients with pOBC who all had chemotherapy (9 neoadjuvant and 27 adjuvant). The 10-year survival rate was 95%. The pCR rate in the 9 neoadjuvant patients was only 67%. It suggests neoadjuvant chemotherapy (NAC) is a reasonable option for OBC patients, particularly for high grade HER2+ and triple negative disease where a pCR is more likely.

Table 2
Treatment groups and OS [9].

Groups	n	5-year OS %	8-year OS (%)
Observation alone	191	56.5 ± 4.8	49.0 ± 5.9
ALND alone	106	76.2 ± 5.0	65.1 ± 6.7
ALND + RT	342	90.8 ± 1.9	84.7 ± 3.6
ALND + Mastectomy ± RT	592	80.0 ± 2.2	72.8 ± 3.2

OS Overall Survival, ALND Axillary lymph node dissection, RT Radiotherapy.

Sentinel node biopsy in occult breast cancer post NAC

Initial studies assessing sentinel node biopsy (SNB) post NAC, the SENTINA and ACOSOG Z1071 (Alliance) trials, reported high false negative rates [41,42]. However, SNB has been subsequently proven to be more accurate in cN1 patients who undergo NAC if - two or more nodes are removed, the clipped node is removed and immunohistochemistry is used. As a result, patients undergoing NAC can be down-staged in the axilla and ALND can potentially be avoided [43–45]. The same could be said for patients with pOBC, particularly if they are already considered to be in a better prognostic group than those patients with T1N1 disease [25,26]. If that is the case it is not unreasonable to consider de-escalating treatment in the axilla ± breast. There are no studies that have specifically addressed this question in this highly selective subset. Treatment at this stage is to still proceed with ALND and in the absence of a clinical trial the authors support this, but in the future, it may be reasonable to only perform a sentinel node biopsy or targeted clearance if a pCR has been achieved. We would not advocate for this with more than 2 nodes clinically or radiologically apparent prior to NAC as it is not feasible to clip multiple nodes.

Conclusion

As diagnostic techniques continue to improve, the incidence of pOBC has decreased to the point where it is rare. cOBC should be worked up with MRI (preferably 3T). NAC should be considered and while further trials need to be performed in this area with more homogeneous cohorts, it may be possible in the context of a pCR to significantly de-escalate axillary surgery. Evidence to date suggests that better outcomes are achieved if the ipsilateral breast is treated and given the equivalent outcomes for whole breast radiation versus surgery, patients can safely avoid mastectomy.

Funding source

There has been no study sponsors involved.

Ethical approval

No ethical approval was required.

Declaration of competing interest

There is no conflict of interest for any of the authors associated.

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