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CLINICAL TRIAL

Immunohistochemically defined subtypes and outcome in occult breast carcinoma with axillary presentation

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Abstract The aim of this study is to evaluate the outcome of occult breast cancer (OBC) in patients with axillary presentation overall and according to the immunohistochemically defined tumour subtypes. We reviewed information on 15,490 consecutive primary breast cancer patients, who underwent surgery at the European institute of oncology between September 1997 and December 2008. Patients with OBC were compared with an equal number of patients with small invasive breast carcinomas (pT1) observed at the same institution during the same period, matched for year of surgery, age, nodal status and biological features. Eighty patients with OBC (study group) and 80 patients with early breast cancer (control group) were identified. There was no significant difference in the disease-free survival (5 years DFS 66 vs. 68% $P = 0.91$) and the overall survival (5 years OS 80 and 86% $P = 0.99$) between the OBC and control groups. A statistically significant worse outcome was observed within the group of OBC for patients with more than four involved lymph nodes and with triple negative tumours. The outcome of OBC patients is comparable with that of matched patients with small sized breast cancer. High risk of relapse and death was observed in OBC patients with triple negative tumours and extensive nodal involvement.

Keywords Axillary · Breast cancer · Triple negative

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Introduction

The primary site of cancer may not be identifiable in patients with biopsy-proven metastatic axillary nodes, in spite of extensive clinical work-up. Possible sources of carcinoma metastatic to the axilla include primary tumours in the lung, ovary, thyroid, pancreas, urogenital tract, or intestine, but axillary involvement in a female patient without any other sign of disease is mostly related to the presence of occult breast cancer (OBC).

The frequency of OBC is reported to be 0.3–1.0%, with peak incidence at around 55 years of age [1–3]. Due to the low number of patients included in published series, the outcome of OBC is still unclear, though a favourable outcome has been reported in small series of patients [4–8]. Previous studies, however, did not use a matched design based both on stage and biological features to allow for imbalances of prognostic factors other than OBC.

Recent studies using DNA microarray profiling have led to the classification of invasive breast cancer subgroups with common molecular features [9–11] and to the recognition that breast cancer is a heterogeneous entity. Several molecular subgroups have been proposed: HER2-overexpressing or oestrogen receptor (ER), progesterone receptors (PgR)-negative tumours, basal-like (ER, PgR HER2 negative disease) and luminal (ER and/or PgR expression) [10, 11].

An Immunohistochemical (IHC) profile based on the extent of expression of ER, PgR and HER2 similarly identifies subgroups of breast cancer patients with different outcome and responsiveness to systemic therapies [12–14].

The present report aims to assess the outcome of patients with OBC according to clinical and biological features. Moreover, we compared the outcome of patients with OBC, with an equal number of patients with small invasive breast carcinomas (pT1) observed at the same institution during the same period, matched for year of surgery, age, nodal involvement and biological features.

Patients and methods

Patients

We reviewed information on consecutive breast cancer patients, whose definitive primary surgery was performed at the European institute of oncology between September 1997 and December 2008. We include amongst these 80 women (study group), in whom the initial presentation was a conspicuous nodule in the axilla, accompanied by a diagnosis of metastatic adenocarcinoma consistent with mammary carcinoma, following biopsy elsewhere. In all cases, both breasts were clinically negative for cancer. Initial work-up was mammography and ultrasonography of both breasts. If these were negative, breast MRI was generally performed. All patients received a careful physical examination of the thyroid, abdomen, lymph nodes and breasts; the skin was also examined visually. If the results of these examinations were unrevealing, liver ultrasound, chest X-ray and bone scan were performed. In a subgroup of patients, CT scan and/or PET scan was also performed. Subsequently, axillary dissection was performed or completed.

For each patient in the study group, we selected from the same database, one matched patient with nodal involvement and with small size tumour of the breast ($\leq$2 cm) (control group).

The variables used to make the randomly assigned matches were as follows: age (within 5 years), number of positive lymph nodes (from 1 to 3, from 4 to 9 and more than 9), hormone receptor status (ER or PgR both negative, ER $<$ 50% or PgR $<$ 50%, ER and PgR both $\geq$ 50%), HER2/neu protein overexpression or gene amplification and year of surgery (within 2 years).

Following surgery, all cases were discussed during the weekly multidisciplinary meeting attended by surgeons, medical oncologists, radiation oncologists and pathologists. The decision for adjuvant systemic treatment was made on the basis of biological features, staging, treatment previously received and comorbidities.

Pathology and immunohistochemistry

In this single institution study, all patients had pathological evaluation performed at the European institute of oncology. Immunostaining for the localization of ER and PgR, HER2 protein and Ki-67 antigen was performed on consecutive tissue sections from the nodal disease.

The following primary antibodies were used: The monoclonal antibody (MAb) to ER (Dako, Glostrup, Denmark at 1/100 dilution), the Mab to PgR (Dako, 1/800), the MIB-1 Mab to the Ki-67 antigen (Immunotech, Marseille, France, 1/1200) and the polyclonal antiserum (Dako, 1/3200) to the HER2 protein [15].

Only nuclear reactivity was taken into account for ER, PgR and Ki-67 antigen, whereas only an intense and complete membrane staining in $>$10% of the tumour cells qualified for HER2 overexpression (3+). FISH assays (using the PathVysion HER2 DNA kit, Vysis–Abbott, Des Plaines, IL) were performed in cases with equivocal (2+) immunohistochemical results to identify cases with gene amplifcation (HER2 to chromosome 17 centromere ratio $\geq$2). The results for ER, PgR and Ki-67 were recorded as the percentage of immunoreactive cells observed amongst at least 2,000 neoplastic cells. The value Ki-67 labelling index (LI) was divided into low ($<$14%) and high ($\geq$14%). [11]. Steroid hormone receptors status was classified as negative (lack of any ER and PgR immunoreactivity, or $<$1% immunoreactive tumour cells), incompletely endocrine responsive (ER and/or PgR $<$ 50% of the cells) or highly endocrine responsive (both ER and PgR $>$ 50% of the cells).

According to himmunohystochemical evaluation we identify four subtypes

Luminal A (ER $>$ 0 or PgR $>$ 0) and (HER2 negative),

Luminal B (ER $>$ 0 or PgR $>$ 0) and (HER2 positive),

HER2- positive (ER = 0 and PgR = 0) and (HER2 positive) and

Triple Negative (ER = 0 and PgR = 0) and (HER2 negative).

Statistical analysis

The end points evaluated were disease-free survival (DFS), overall survival (OS), cumulative incidence of loco-

regional recurrence (CI-LR) and distant recurrence (CI-D), all measured from the date of surgery.

DFS was defined as the time from surgery to events such as relapse (including ipsilateral breast recurrence), appearance of a second primary cancer (including contralateral breast cancer), or death, whichever occurred first.

OS was defined as the time from surgery until the date of death (from any cause).

The DFS and OS functions were estimated using the Kaplan–Meier method. The log-rank test was used to assess differences between groups.

The CI-LR and CI-D were defined as the time from the date of surgery to a loco-regional recurrence and a distant metastases, respectively.

The CI-LR and CI-D curves functions were estimated according to methods described by Kalbfleisch and Prentice [16], taking into account the competing causes of recurrence. The Gray's test was used to assess cumulative incidence differences between groups [17].

The hazard ratio (HR) comparing OBC patients (study group) and those with small tumours (the matched control group) was estimated with a Cox proportional hazards model controlled for age, number of positive lymph nodes, hormone receptor, and HER2 status and year of surgery.

The prognostic impact of several factors in the study group on DFS, OS and cause-specific hazard was evaluated using multivariable Cox proportional hazards regression models and expressed as HR with 95% confidence interval (CI). All analyses were carried out with the SAS software (SAS Institute, Cary, NC) and the R software (http://cran.r-project.org/) with the cmprsk package developed by Gray (http://biowww.dfci.harvard.edu/_gray).

All reported *P*-values are two-sided.

Results

A total of 15,490 consecutive patients with breast cancer who had definitive surgery, referred for interdisciplinary evaluation between September 1997 and December 2008 and included in a prospective quality controlled data-base, were analysed. We excluded a priori patients that were presented with metastatic disease, other previous primary tumours, previous contralateral breast cancer, recurrent disease at presentation and primary chemotherapy. We found 80 patients with OBC (study group) and 80 patients with early breast cancer (control group) and they were identified.

Table 1 reports the clinical and biological features of the study and control groups. The two groups were homogenous. The only differing variable was the presence of invasive tumour size in the control group, with 86% of the patients having a tumour size ranging from 1 cm to 2 cm. 26% of the patients in both groups showed more than 10 positive lymph nodes, and a high percentage of patients (58%) had non-endocrine responsive disease and HER2 was over-expressed in 25% of patients.

Table 2 shows the local treatment for OBC patients and control group.

Four patients and 30 patients in the study group underwent monolateral mastectomy and conservative surgery, respectively. Adjuvant radiotherapy was proposed to 91% of patients in OBC.

For patients of control group, 66 patients underwent conservative surgery, followed by adjuvant radiotherapy.

A comparable number of patients in the two groups received adjuvant therapy (chemotherapy for 52 and 46% of patients in OBC and control group, respectively; combined hormonal and chemotherapy for 34% of the patients in OBC and 34% in the control group).

After a median follow-up of 6.1 years (range 1–12 years), we observed 24 and 19 events related to breast cancer in OBC and control group, respectively.

The Kaplan–Meier curves for DFS, OS, CI-LR and CI-D recurrence by group are displayed in Fig. 1.

There was no significant difference in DFS (5 years DFS 66% vs. 68% $P = 0.91$) and OS (5 years OS 80 and 86% $P = 0.99$) between the OBC and control groups.

Figure 2 reports DFS for OBC according to patients characteristics. The 5 year DFS was 52% in the triple negative subtype compared with 76% in the others subtypes ($P = 0.012$). Worse DFS was observed for patients with more than four positive lymph node compared with less than four ($P = 005$). The high number of positive lymph node also was correlated with worse OS ($P = 0.001$) and risk of distant metastasis ($P = 0.005$), triple negative subtype had a higher risk of LR recurrence ($P = 0.025$) as reported in Table 3.

Multivariate analysis

The independent impact on DFS, OS, risk of LR recurrence and risk of distant metastasis was assessed for various clinico-pathological features of OBC patients. The results are displayed in Table 4.

The presence of more than four positive lymph nodes was independently correlated with a worse outcome (HR 4.82; 95% CI 1.94–11.96 for DFS. HR 12.4; 95% CI 2.57–60.14 for OS HR 10.8; 95% CI 2.13–55.22 for risk of distant metastasis). Triple negative breast cancer subtype was associated with worse DFS (HR 4.38; 95% CI 1.68–11.41) increased risk of death (HR 6.44; 95% CI 1.29–32.28.) and subsequent local event (HR 13.37; 95% CI 1.59–11.27).

Table 1 Patient characteristics

	Study group (Occult BC)				Control group (pT1 BC)			
	No.	%	Median	Range	No.	%	Median	Range
Matching variables								
Age			54	29–80			54	30–77
<35	4	5			3	4		
35–49	29	36			29	36		
50–59	21	26			24	30		
60+	26	33			24	30		
No. of positive lymph nodes			3	1–65			3	1–59
1–3	42	53			42	53		
4–9	17	21			17	21		
10+	21	26			21	26		
ER/PgR								
Both 0	46	58			46	58		
ER < 50 or PgR < 50	23	29			23	29		
ER ≥ 50 and PgR ≥ 50	21	26			21	26		
HER2 status								
Positive	20	25			20	25		
Negative	59	74			59	74		
Unknown	1	1			1	1		
Year of surgery			03	97–08			03	97–08
≤2000	24	30			18	23		
01–04	26	33			30	38		
05–08	30	38			32	40		
Other variables								
Menopausal status								
Premenopausal	34	43			34	43		
Postmenopausal	46	58			46	58		
In situ component								
No	65	81			72	90		
Yes	15	19			8	10		
Tumour size								
≤0.5 cm	–	–			2	3		
0.5–1 cm	–	–			9	11		
1–2 cm	–	–			69	86		
Grade								
1–2	2	3			27	34		
3	16	20			51	64		
Unknown	62	78			2	3		
Ki-67								
<14%	3	4			13	16		
≥14%	31	39			65	81		
Unknown	46	58			2	3		
PVI								
Absent	23	29			37	46		
Present	1	1			18	23		
Focal	3	4			2	3		
Diffuse	1	1			23	29		
Unknown	52	65			–	–		

Study and control group

BC breast cancer, *ER* oestrogen receptors, *PgR* progesterone receptors and *PVI* perivascular invasion

Table 2 Local and systemic treatments

	Study group (Occult BC)		Control group (pT1 BC)	
	No.	%	No.	%
Surgery				
Only axillary dissection	46	58	–	–
Conservative	30	38	66	82
Mastectomy	4	5	14	18
Adjuvant radiotherapy				
Yes	73	91	72	90
No	7	9	8	10
Adjuvant treatment				
Nil	4	5	6	7
ET	7	9	10	13
CT	42	52	37	46
CT + ET	27	34	27	34

Study and control group

BC breast cancer, *ET* endocrine therapy and *CT* chemotherapy

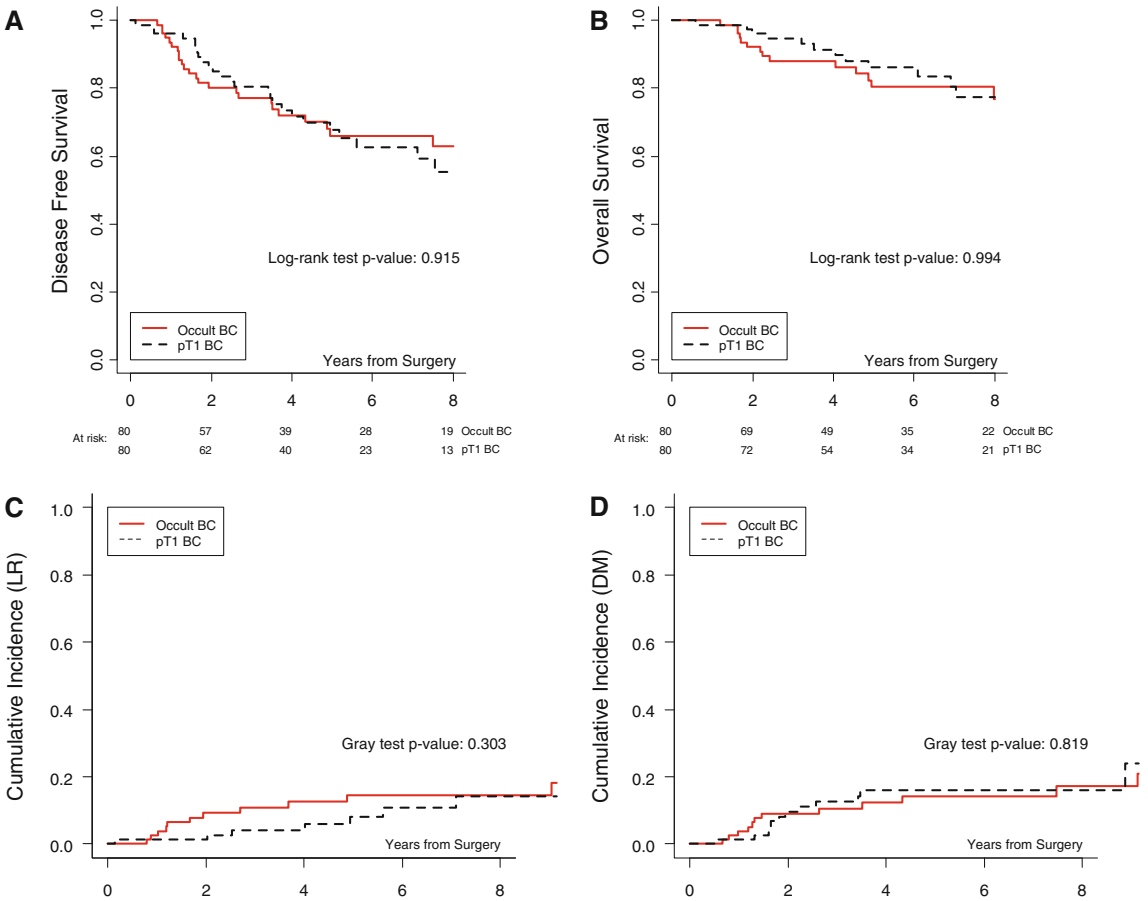

Fig. 1 Disease-free survival (**a**), overall survival (**b**), cumulative incidence of loco-regional events (**c**), and distant metastases (**d**). Study and control group

Discussion

The involvement of axillary lymph nodes still represents the most reliable prognostic factor for patients with operable breast cancer. Few studies on a large number of patients have investigated the prognostic significance of involvement of axillary lymph nodes in patients with OBC.

Newman et al. [4] reported a better outcome for patients with occult disease, if compared with patients with stage II or III breast cancer [4]. Other authors reported a survival

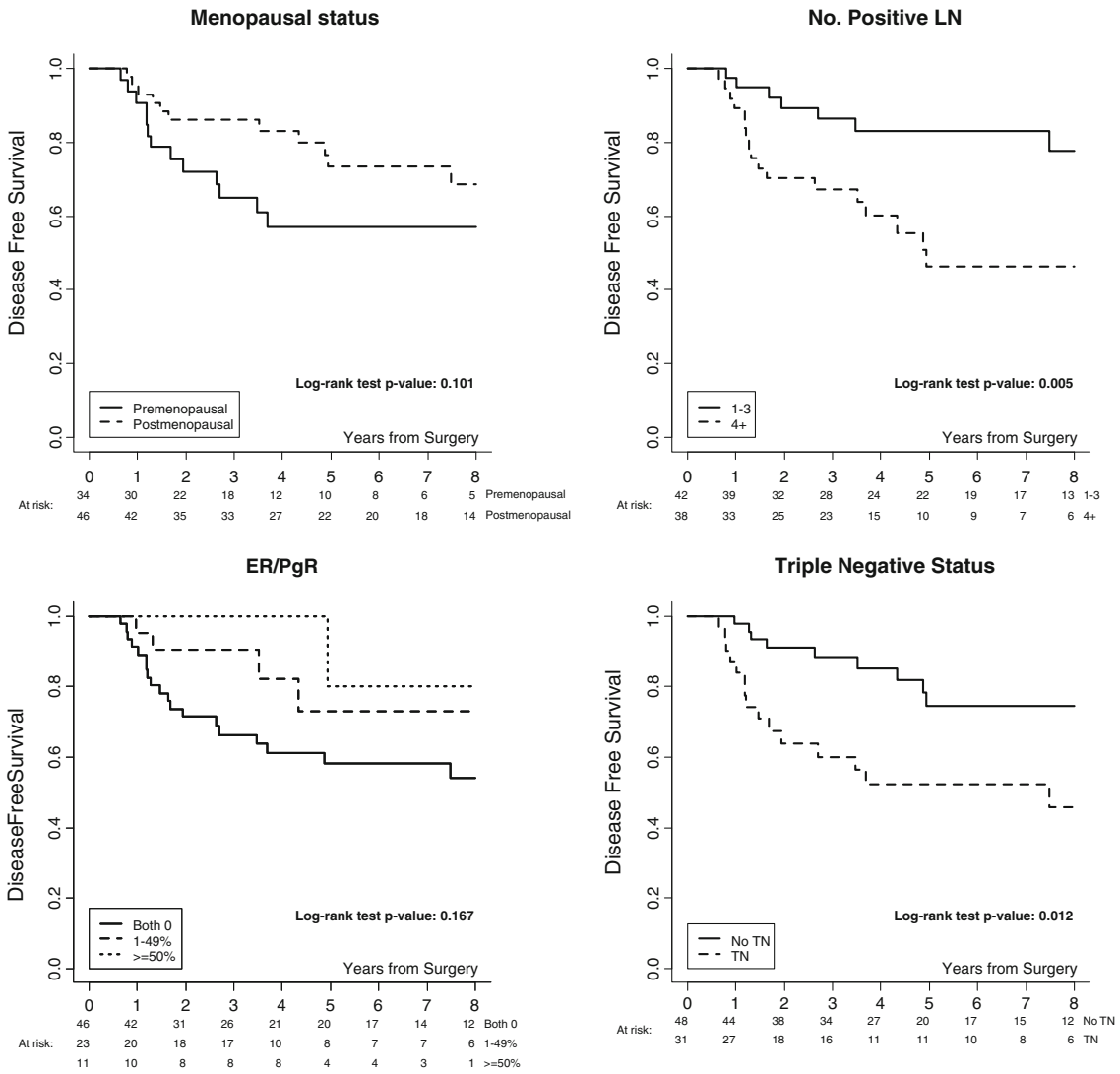

Fig. 2 Disease-free survival by patients' characteristics. Occult BC group

for patients with OBC similar to stage-matched patients with node positive BC [5–8]. Conversely, Svastics and Jackson indicated a worse prognosis for occult disease [18, 19]. Data from past series, however, were derived from small series of patients, with several characteristics of the disease collected in the earlier period, when neither systemic treatments or various prognostic, and predictive factors were available as they are today.

The present study, based on prospectively defined and quality controlled databases, provides the largest population with long follow-up (6.1 years) on this subject. It provides useful insights into the treatment and prognosis of OBC because it is based on a large number of patients, collected in a relatively short time and thus allows adoption of modern procedures. The pathologists, surgeons and medical oncologists employed consistent approaches during the years of reference, which is a major strength of the current analysis. All the patients received a local treatment that included mastectomy or radiotherapy of the ipsilateral breast, after the diagnosis of OBC.

Moreover, no patient with invasive breast cancer detected at surgery was classified as OBC in this study. In fact, previous studies focusing on OBC also evaluated patients with histopathological identification of invasive carcinoma on the breast. A review focusing on 689 patients included in 24 retrospective series of OBC was recently reported [20]. Amongst a total of 446 patients managed with mastectomy, an occult breast primary tumour was eventually identified histologically in 321 patients (72%).

We observed a similar outcome in terms of both DFS and OS for patients who presented with OBC compared with those, who had a small breast tumour matched for both clinical and biological features. We selected patients with small tumours, to avoid interference in the analysis of other classical prognostic features such as tumour size.

Table 3 Five years disease-free survival (DFS), overall survival (OS), cumulative incidence of locoregional recurrence (CI-LR) and of distant metastases (CI-DM), by patients' characteristics

Variable	Level	No. at risk	5 years DFS (95% CI)	*P*	5 years OS (95% CI)	*P*	5 years CI-LR (95% CI)	*P*	5 years CI-DM (95% CI)	*P*
All patients		80	66 (53–76.3)		80.4 (68.3–88.3)		14.5 (8.1–26.1)		14.3 (8–25.7)	
Menopausal status	Premenopausal	34	57.1 (37.4–72.7)	0.101	76.4 (56.3–88.2)	0.365	23.3 (12.1–45)	0.024	15.7 (7–35.3)	0.89
	Postmenopausal	46	73.4 (55.6–84.9)		83.7 (66.9–92.5)		7.7 (2.6–23.4)		13.2 (5.8–30.3)	
In situ component	No	65	63 (48.6–74.4)	0.514	76.9 (63.2–86)	0.078	17.5 (9.8–30.9)	0.39	13.6 (7.1–26.1)	0.893
	Yes	15	79.6 (37.1–94.9)				0 (–)		20.4 (5.5–75.5)	
No positive LN	1–3	42	83.1 (65.9–92.1)	0.005	97.4 (83.2–99.6)	0.001	13.6 (6–30.9)	0.653	0 (–)	0.005
	4+	38	46.2 (27.1–63.4)		60 (39–75.8)		16.5 (7.2–37.8)		30 (17.5–51.3)	
ER/PgR	0	46	58.2 (41.8–71.5)	0.167	76.2 (60–86.5)	0.343	23.5 (13.6–40.7)	0.059	13.5 (6.4–28.5)	0.785
	ER or PgR < 50	23	73.1 (41–89.6)		86.8 (54.1–96.8)		0 (–)		26.9 (11–65.6)	
	ER> and Pgr ≥ 50	11	80 (20.4–96.9)		80 (20.4–96.9)		0 (–)		0 (–)	
HER2	Positive	20	69.8 (41.3–86.4)	0.238	68.8 (40–85.9)	0.397	7 (1.1–46.1)	0.143	18 (6.3–50.9)	0.868
	Negative	59	64.1 (48.7–76)		84.4 (70.8–92)		17.3 (9.5–31.6)		13.2 (6.6–26.4)	
HER2/ER/PgR	HER2−/Er/Pgr−	31	52.4 (32.9–68.6)	0.092	79.3 (59.5–90.2)	0.437	30.8 (17.8–53.4)	0.025	13 (5.2–32.6)	0.993
	HER2−/Er/Pgr+	28	78.1 (49.6–91.6)		88.6 (59.5–97.2)		0 (–)		14.1 (4.8–41.7)	
	HER2+/Er/Pgr−	14	68.6 (35.9–87)		68.6 (35.9–87)		8.6 (1.3–55.7)		15.7 (4.4–56.6)	
	HER2+/Er/Pgr+	6	66.7 (5.4–94.5)		66.7 (5.4–94.5)		0 (–)		33.3 (6.7–100)	

Occult BC group

BC breast cancer, *LN* lymph nodes, *ER* oestrogen receptors; and *PgR* progesterone receptors

Table 4 Multivariable Cox regression analysis for disease-free survival (DFS), overall survival (OS), cause-specific hazard for loco-regional (CSH-LR) and distant metastases (CSH-DM) recurrence

	DFS HR (95% CI)	*P*	OS HR (95% CI)	*P*	CSH-LR HR (95% CI)	*P*	CSH-DM HR (95% CI)	*P*
Menopausal status								
Pre vs. Post	1.32 (0.59–2.94)	0.499	1.13 (0.37–3.44)	0.826	3.57 (0.85–15)	0.082	0.89 (0.26–2.96)	0.844
No Positive LN								
4+ vs. 1–3	4.82 (1.94–11.96)	0.001	12.42 (2.57–60.14)	0.002	2.49 (0.66–9.36)	0.176	10.85 (2.13–55.22)	0.004
HER2/ER/PgR								
HER2−/Er/Pgr−vs. HER2−/Er/Pgr+	4.38 (1.68–11.41)	0.003	6.44 (1.29–32.28)	0.023	13.37 (1.59–112.7)	0.017	2.54 (0.64–10.02)	0.184
HER2+/Er/Pgr−vs. HER2−/Er/Pgr+	1.03 (0.3–3.6)	0.96	3.47 (0.63–19.06)	0.152	1.65 (0.1–26.47)	0.724	0.75 (0.14–4.09)	0.735
HER2+/Er/Pgr+ vs. HER2−/Er/Pgr+	0.58 (0.06–5.22)	0.627	3.61 (0.31–42.57)	0.308	0 (0)	0.993	1.27 (0.13–12.14)	0.836

Occult BC group

BC breast cancer, *LN* lymph nodes, *ER* oestrogen receptors and *PgR* progesterone receptors

In this study, we demonstrated a statistically significant worse outcome in terms of both DFS (HR 4.82) and OS (HR 12.4) for patients with OBC, who presented with more than four positive axillary nodes compared with those who had less nodal involvement.

Recently, different subtypes of breast cancer have been identified, based on gene expression profiling, with differential responsiveness to treatments and outcome [9–11]. Due to the fact that it is not always feasible to obtain gene expression profiles, a simplified classification based upon immunohistochemical evaluation of ER, PgR, Ki-67 and HER2 was recently adopted [12–14]. Although subtypes defined by clinico-pathological criteria are similar to but not identical to intrinsic subtypes, immunohistochemistry might be considered a useful surrogate for identifying the molecular subtypes of breast cancer. The use of this classification appeared useful to define different prognostic subgroups and different responsiveness to the adjuvant treatment received [13, 14].

In the present analysis, patients with OBC of the triple negative subtype had the highest risk of recurrence and death. In particular, at the multivariate analyses, the triple negative subtype was significantly associated with worse prognosis in terms of DFS, OS and risk of loco-regional recurrence (HR 4.38, HR 6.44, and HR 13.37), if compared with luminal subtypes. Emerging data on the clinical implications of invasive ductal carcinoma with the triple negative phenotype indicated an aggressive course of the disease [21, 22]. Despite the widespread acknowledgement of the poor clinical outcome, the prognostic value of the triple negative subtype within the subgroup of OBC continues to raise uncertainty. It is noteworthy that the biological features were evaluated on axillary nodes indicating a prognostic role for biological features performed on nodal tissues in OBC. In general, the concordance of the biological features (HER-2 status, ER and PgR expression) between the primary tumour and ipsilateral axillary lymph node metastases is high, ranging from 78 to 90% [23–26].

However, this is the first report that indicated that in OBC, the evaluation of biological features in the axillary nodes maintains a significant prognostic role.

The finding that subgroups of patients remain at substantial risk of relapse was observed in a population subjected to an adjuvant therapy programme might have interfered with the outcome**.** It is noteworthy that in the present analysis medical oncologists used consistent approaches during the years of reference. The adjuvant treatment proposed was largely based on the degree of nodal involvement, as well as on known prognostic features according to the St. Gallen consensus conference guidelines [27, 28].

The efficacy of adjuvant systemic therapy for early breast cancer depends on various variables, which include

features of the tumour of the patient and the treatment itself. The main issue to be discussed is whether the OBC presentation should be a factor influencing the treatment choice, possibly affecting decisions about whether different systemic treatment should be given. We report that the outcome of OBC patients is comparable with that of stage and subtype-matched patients with breast cancer. Higher risk of relapse and death was observed in OBC patients with triple negative subtype and extensive (more than four) nodal involvement. As for patients with early breast cancer, the therapeutic choices for patients with OBC should be based on clinical and biological disease features.

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