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Original Research

Contribution of endocrine therapy in oestrogen receptor-positive pT1a-b breast cancer: Results of a retrospective study



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KEYWORDS

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Multivariate analysis;
Retrospective studies;
Disease-free survival

Abstract Introduction: Few data have been reported regarding endocrine therapy (ET) in patients with small pT1a-b ER-positive breast cancer (BC). Thus, we conducted a study to detect possible survival improvements due to ET in such patients.

Methods: Our retrospective observational study included 5545 patients with pT1a-b ER-positive BC treated in 15 French centres, excluding patients with HER2-positive status, neoadjuvant chemotherapy, ER-negative status, unknown pN status or in situ BC. We estimated disease-free survival (DFS), recurrence-free survival (RFS) and overall survival (OS) via univariate analysis and multivariate Cox regression.

Results: Most patients (80.3%: 4453) received ET and—when compared to those without ET—experienced increases of 2.5% and 3.3% in DFS and 1.9% and 4.3% in RFS after 5 and 7 years of follow-up, respectively, with little difference in OS. In Cox regression analysis, no ET was significantly associated with decreased DFS (hazard ratio, HR = 1.275, $p = 0.047$, 95% CI[1.003–1.620]) but not OS or RFS in all patients, while in 2363 patients with pT1a-b ER-positive grade 2–3 BC, no ET was significantly associated with decreased DFS (HR = 1.502, $p = 0.049$, 95% CI[1.001–2.252]), but not OS (HR = 1.361, $p = 0.272$). ET omission was not significantly associated with decreased survival in 3047 patients with pT1a-b ER-positive grade 1 BC.

Conclusion: Our results indicate that while ET provided a beneficial impact on survival to patients with pT1a-bN0 ER-positive BC—and especially in those with grade 2–3 tumours—no such impact was observed in grade 1 tumours. Consequently, ET should be discussed with these patients, particularly in those with pT1a grade 1 tumours.

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1. Introduction

Survival improvements have been well documented concerning the use of endocrine therapy (ET) in patients with oestrogen receptor (ER) positive breast cancer (BC), regardless of tumour size, patient age or type of ET [1–6]. Currently, ET has an overall favourable toxicity profile, but may still induce significant side-effects that can negatively impact a patient's quality of life. These include rare but potentially life-threatening events such as endometrial carcinoma, thromboembolic (tamoxifen) and cardiovascular events, osteoporosis and increased fracture risk (aromatase inhibitors). Accordingly, ET for small tumours is indicated in various guidelines but may be discussed with the patient, particularly concerning pT1a tumours. That being said, few data have been reported regarding patients with small pT1a-b tumours, and we noted in a previous study that tumour size may not be the main prognostic factor in T1 BC [7]. ET for ER-positive tumours may be avoid with patients presenting pT1a-b tumours without axillary involvement, but is rarely avoid for pN1 or even pN1mi tumours. Similarly, while the need for trastuzumab-based adjuvant chemotherapy may be disputed in pT1a-b ER-positive/HER2-positive tumours [8,9], ET is rarely omitted in small node-negative ER-positive/HER2-positive BC. With this in mind, we analysed the impact of ET in all patients with endocrine-sensitive pT1a-b BC, as well as additional subsets of patients with pN0, HER2-negative, or grade 2–3 disease, excluding those with unknown HER2 status in these subsets. We report herein the results of our

multicentre retrospective study with the goal of detecting possible improvements in survival from ET for patients with pT1a-b ER-positive tumours.

2. Methods and materials*2.1. Patients*

We retrospectively analysed a cohort of 23,134 patients with BC and with pT1a-b ER-positive tumours across 15 centres. Our exclusion criteria included: in situ BC, neoadjuvant chemotherapy, ER-negative status (ER $\geq 10\%$ was considered as positive), unknown pN status or HER2-positive status. Our analysis included age, tumour size (pT), Scarff Bloom Richardson (SBR) grade, tumour histology, HER2 status, lymphovascular invasion (LVI), lymph node status (pN), axillary and breast surgery, adjuvant chemotherapy, treatment period (1999–2003, 2004–2006, 2007–2009 and ≥ 2010) and treatment centre. All patients, except those lost to follow-up, were followed for a minimum of 6 years. Informed consent was waived since all data were de-identified and collected retrospectively from each centre.

2.2. Statistical analysis

Factors associated with ET were determined via binary logistic regression analysis. We performed survival analyses via univariate and multivariate Cox regression analyses of disease-free survival (DFS; defined as the length of time from the date of surgery to an event including death, local recurrence, axillary recurrence,

metastasis, or contralateral BC), recurrence-free survival (RFS; date of surgery until an event including local recurrence, axillary recurrence, or metastasis) and overall survival (OS; date of surgery until death from any cause) for one or more of the following groups: (1) all patients, (2) those with pN0 or pN0(i+) status, (3) those with HER2-negative status and (4) patients with grade 2–3 tumours. We assessed the associations of BC outcomes with ET via Kaplan–Meier analyses and used Cox regression analysis to assess the association of event rate ratios with ET.

In order to balance differences in prognostic variables associated with ET, we generated 1:1 ET and no ET matched cohorts. Coefficients of a logistic regression adjusted for age, tumour size, pN status, histology, LVI, axillary surgery, breast surgery, AC, regional node irradiation, periods and tumour grade were used to compute a propensity score. Patients with ET were then matched on this score to no ET patients using nearest-neighbour matching without replacement [10,11]. Further details on propensity score matching approaches have been provided (Supplementary Fig. 1).

Patient characteristics according to ET in the matched population have been reported (Supplementary Table 1). The impact of ET on DFS, MFS and OS was assessed in this matched population by log-rank tests stratified on the pairs [12].

3. Results

3.1. Patient characteristics

Of the 23,134 patients with BC treated in participating centres, 5545 patients were included in the study. Of these, 3999 patients were HER2-negative while 1546 patients had unknown HER2 status (Fig. 1).

The clinical and pathological characteristics according to ET were recorded for 1064 pT1a tumours and 4481 pT1b tumours (Table 1). A majority of patients (80.3%: 4453) received ET, with a significantly higher rate of ET administered during the first time period compared to the last three periods combined (82.2%: 1432/1742 versus 79.4%: 3021/3,803, respectively; $p < 0.02$) for both pT1a (74.27%: 224/300 versus 72.9%: 557/764, respectively; nonsignificant) and pT1b (83.8%: 1208/1442 versus 81.1%: 2464/3039, respectively; $p < 0.05$) tumours. The administration of ET also differed significantly between treatment centres ($p < 0.0001$, Table 1), ranging from 41% to 100%, according to univariate analysis. Sentinel lymph node biopsies determined the axillary lymph node status of 5015 patients (90.4%) with complementary axillary lymph node dissection in 1039 patients (20.7%). The pathological axillary lymph node status was pN0 or pN0(i+) in 4782 patients (86.2%), pN1mi in 350 patients (6.3%) and pN1macro in 413 patients (7.4%).

Patients with ET had proportionally fewer recurrences than those without (4.8% versus 7.4%, respectively; $p = 0.001$), though when analysed according to type, only local recurrence showed a significant difference (1.5% versus 4.8%, respectively; $p < 0.0001$, Supplementary Table 2).

Patients who received adjuvant chemotherapy had clinical and biological characteristics that highlight a higher risk of recurrence (Supplementary Tables 3–4 for univariate and multivariate analysis) and patients without ET received lesser adjuvant chemotherapy (OR = 0.315, $p < 0.0001$). In matched population, there was no significant difference of adjuvant chemotherapy rate. Patients with axillary lymph node dissection had clinical and biological characteristics that highlight a higher risk of recurrence (Supplementary Tables 5–6 for univariate and multivariate analysis).

3.2. Survival analysis in all patients

Binary logistic regression analysis identified factors significantly associated with ET, which included age, grade, tumour histology, pN status, negative or unknown HER2 status and time period (Table 2).

The median follow-up for all patients was 58.62 months (mean: 61.19, 95% confidence interval (CI) [60.1–62.3]). There were 194 events within the first 5 years of follow-up, with 2647 patients at risk of an event (47.7%) at 5 years. According to Kaplan–Meier analysis, the 5-year DFS rates in patients who either had or had not received ET were 95.7% (SD: 0.4) versus 93.2% (SD: 0.9), while 7-year DFS was 91.2% (SD: 0.6) and 87.9% (SD: 1.5), respectively (Log Rank: 0.052, Fig. 2).

The RFS rates for those with or without ET at 5 and 7 years were 97.7% (SD: 0.3) versus 95.8% (SD: 0.7) and 95.5% (SD: 0.5) versus 91.2% (SD: 1.3), respectively (Log Rank: 0.016, Fig. 3).

Overall survival rates in patients who had or had not received ET at 5 and 7 years were 97.7% (SD: 0.3) versus 97.2% (SD: 0.6) and 96.0% (SD: 0.4) versus 96.5% (SD: 0.7), respectively (Log Rank: 0.409, Supplementary Fig. 2).

According to univariate analysis, factors significantly associated with decreased DFS included no ET, grade, LVI, HER2 status unknown, mastectomy and age; while OS and RFS included grade, LVI, and age and no ET, grade, LVI, mastectomy, age and pT1b, respectively (Supplementary Table 7).

In Cox regression analysis stratified according to these factors and pN status, no ET was significantly associated with a decrease in DFS (hazard ratio, HR: 1.275, $p = 0.047$, 95% CI [1.003–1.620]; Table 3, Fig. 4) but not OS (HR: 1.179, $p = 0.349$, 95% CI [0.835–1.663]; Table 4) or RFS (HR: 1.306, $p = 0.093$, 95% CI [0.957–1.782]; Table 5) in all patients. Other significant factors for reduced DFS included LVI, HER2 status unknown, age ≥ 75 years old, and pN1

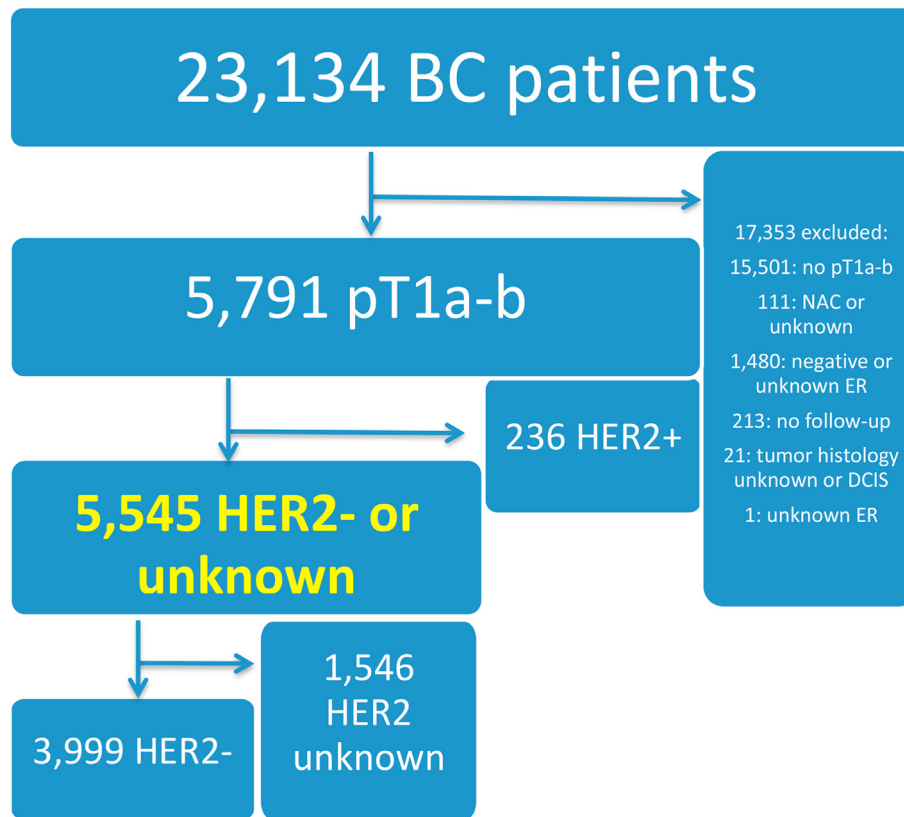


Fig. 1. Flowchart of patient inclusion and exclusion, Abbreviations: NAC; neoadjuvant chemotherapy, DCIS, ductal carcinoma in situ.

macrometastases; while significant factors for OS and RFS included grade 3, age ≥ 75 years old, and pN1 macrometastases; and LVI, age of 50.1–74.9 years and pT1b tumours, respectively.

There were no significant associations between no ET and decreased DFS (HR: 1.200, $p = 0.267$, 95% CI [0.870–1.655]), RFS (HR: 1.010, $p = 0.964$, 95% CI [0.650–1.569]) or OS (HR: 1.386, $p = 0.157$, 95% CI [0.882–2.176]) in 3999 patients with HER2-negative status (patients with unknown HER2 status excluded; Table 6).

Based on the ET propensity score, 1318 patients with ET were matched to 761 patients without ET. The survival analysis of these cohorts revealed no prognostic impact on OS (Supplementary Fig. 3A), DFS (Supplementary Fig. 3B) or RFS (Supplementary Fig. 3C).

3.3. Survival analysis in specific subsets of patients according to tumour grade, size and nodal status

No ET was significantly associated with decreased DFS (HR: 1.502, $p = 0.049$, 95% CI [1.001–2.252]; Table 3, Fig. 5), but not OS (HR: 1.361, $p = 0.272$, 95% CI [0.785–2.360]; Table 4) or RFS (HR: 1.330, $p = 0.251$, 95% CI [0.817–2.164]; Table 5) in multivariate analysis of 2363 patients with pT1a-b ER-positive grade 2–3 tumours.

Whereas in 3047 patients with pT1a-b ER-positive grade 1 tumours, there were no significant associations between ET omission and decreased DFS, OS or RFS. These results were maintained upon stratifying the propensity score-matched cohort according to grade with decreased DFS (HR: 1.981, $p = 0.034$, 95% CI [1.044–3.758]; Supplementary Fig. 3F), but not OS (HR: 2.201, $p = 0.102$, 95% CI [0.856–5.660]; Supplementary Fig. 3E) or RFS (HR: 1.648, $p = 0.180$, 95% CI [0.793–3.423]; Supplementary Fig. 3G) in the 495 patients with pT1a-b ER-positive grade 2–3 tumours, whereas in 1584 patients with pT1a-b ER-positive grade 1 tumours, there were no significant associations between ET omission and decreased OS, DFS, or RFS (Supplementary Fig. 3H, I, and J).

In 4782 pN0 or pN0(i+) patients (Table 7), there was no significant association between ET omission and DFS (HR: 1.188, $p = 0.348$, 95% CI [0.829–1.703]) or OS (HR: 1.210, $p = 0.318$, 95% CI [0.833–1.758]) or RFS (HR: 1.363, $p = 0.082$, 95% CI [0.961–1.933]). This was also the case in 413 patients with pN1macro where only 34 patients had not received ET.

Comparison of pT1a versus pT1b tumours did not reveal any significant difference for either DFS (HR: 0.846, $p = 0.180$, 95% CI [0.663–1.080]) or OS (HR: 1.006, $p = 0.976$, 95% CI [0.695–1.455]).

Table 1
Patient characteristics according to endocrine therapy.

Endocrine therapy		Yes		No		χ^2 P
		Nb	%	Nb	%	
Age	≤40	152	3.4	40	3.7	0.004
	40.1–50	801	18.0	206	18.9	
	50.1–74.9	3242	72.8	750	68.9	
	≥75	257	5.8	93	8.5	
pT	pT1a	781	17.5	283	25.9	<0.0001
	pT1b	3672	82.5	809	74.1	
Grade	1	2270	51.0	777	71.2	<0.0001
	2	1886	42.4	255	23.4	
	3	204	4.6	18	1.6	
	Unknown	93	2.0	42	3.9	
Histology	Ductal	3408	76.5	897	82.1	<0.0001
	Lobular	537	12.1	120	11.0	
	Mixt	64	1.4	2	0.2	
	Others	444	10.0	73	6.7	
pN status	pN0	3623	81.4	1022	93.6	<0.0001
	pN (i+)	122	2.7	15	1.4	
	pN1mi	329	7.4	21	1.9	
	pN1 macro	379	8.5	34	3.1	
HER2 status	HER2 <0	3251	73.0	748	68.5	0.002
	Unknown	1202	27.0	344	31.5	
LVI	No	3425	76.9	880	80.6	0.004
	Yes	308	6.9	48	4.4	
	Unknown	720	16.2	164	15.0	
Axillary surgery	SLNB	3145	70.7	831	76.2	<0.0001
	SLNB + ALND	952	21.4	87	8.0	
	ALND	354	8.0	173	15.9	
Breast surgery	Conservative	4006	90.0	898	82.2	<0.0001
	Mastectomy	391	8.8	87	8.0	
	Unknown	56	1.3	107	9.8	
Chemotherapy	Yes	610	13.7	39	3.6	<0.0001
	No	3843	86.3	1053	96.4	
RT	No	210	53.7	54	62.1	0.097
Mastectomy	Yes	181	46.3	33	37.9	
RNI	No	2977	81.0	918	96.9	<0.0001
	Yes	697	19.0	138	13.1	
Time periods	1999–2003	1432	33.2	310	28.4	<0.0001
	2004–2006	1390	31.2	390	35.7	
	2007–2009	998	22.4	201	18.4	
	≥2010	633	14.2	191	17.5	
Centre						<0.0001

Abbreviations: LVI, lymphovascular invasion; SLNB, sentinel lymph node biopsy, ALND, axillary lymph node dissection; RT, radiation therapy; RNI, regional node irradiation.

4. Discussion

Among patients with ER-positive pT1a-b BC, those who had received ET experienced a 2.5% and 3.3% increase in DFS and a 1.9% and 4.3% increase in RFS after 5 and 7 years of follow-up, respectively, with little to no difference in OS, compared to patients that had not received ET. This benefit in DFS was confirmed via Cox regression analysis stratified according to ET administration and other significant factors, such as LVI, unknown HER2 status, age ≥75 years old and pN1 macrometastases. Furthermore, no ET was significantly associated with reduced DFS in both all patients and a subset of patients with grade 2–3 tumours. However, in a subset of patients with grade 1 tumours,

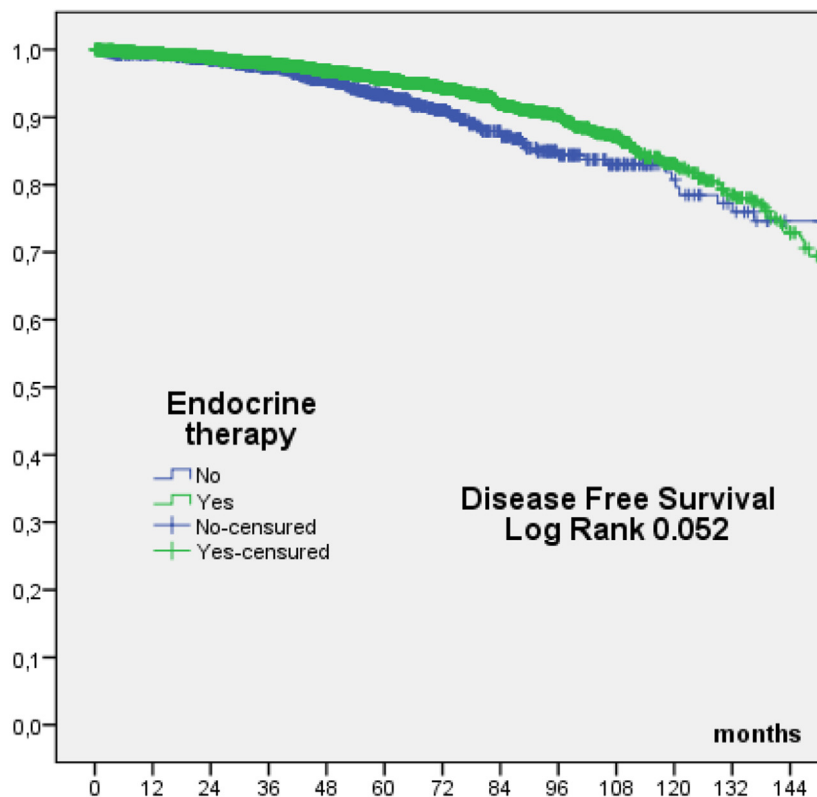
Table 2
Factors associated with endocrine therapy in binary logistic regression.

		p	Odds ratio	CI 95%	
				Inferior	Superior
Age	≤40		1		
	40.1–50	0.194	1.308	0.872	1.962
	50.1–74.9	0.015	1.609	1.097	2.361
	≥75	0.823	1.053	0.669	1.658
Tumour Size	>5 versus ≤ 5 mm	<0.0001	1.468	1.237	1.742
	Grade		1		
Grade	1		1		
	2	<0.0001	2.726	2.311	3.215
	3	<0.0001	4.329	2.603	7.199
	No grade	0.001	4.945	1.922	12.72
Histology	Ductal		1		
	Lobular	0.857	1.021	0.814	1.280
	Mixt	0.004	8.239	1.934	35.10
	Others	<0.0001	2.345	1.781	3.088
pN status	pN0		1		
	pN (i+)	0.015	2.019	1.146	3.556
	pN1mi	<0.0001	4.977	3.121	7.936
	pN1 macro	<0.0001	2.889	1.988	4.199
HER2	Unknown versus < 0	<0.0001	0.613	0.513	0.733
	LVI		1		
LVI	Yes	0.712	1.067	0.757	1.505
	Unknown	0.099	1.189	0.968	1.460
	Surgery		1		
Surgery	Conservative		1		
	Mastectomy	0.594	0.931	0.715	1.211
Periods	1999–2003		1		
	2004–2006	0.514	0.939	0.779	1.133
	2007–2009	0.097	0.827	0.660	1.035
	≥2010	<0.0001	0.544	0.428	0.693

Abbreviations: LVI, lymphovascular invasion; SLNB, sentinel lymph node biopsy, ALND, axillary lymph node dissection; RT, radiation therapy; RNI, regional node irradiation.

there was no prognostic impact observed on DFS, OS or RFS. These findings were confirmed in both subsets of patients in propensity scoring stratified according to grade.

While most guidelines recommend adjuvant ET in almost all patients with invasive ER-positive BC [13], the prescribing of ET in subcentimeter tumours lacks a strong consensus as reflected by our results. A significantly higher rate of ET was administered to patients with pT1b tumours compared to pT1a tumours (81.9% versus 73.4%, respectively), and to those with pN1 disease (94.0% for pN1mi and 91.8% for pN1macro) compared to pN0 disease (78.0% for pN0 and 89.0% for pN0(i+)), even though we found no difference in DFS and OS between pT1a and pT1b tumours in multivariate analysis. This lack of consensus was further illustrated by a significant difference in ET administration according to treatment centre. Interestingly, ET was also administered less frequently after the year 2010 compared to the initial period of 1999–2003 (OR: 0.544, 76.8% versus 82.2%, respectively, $p = 0.002$), which may be due to recent efforts aimed at deescalating therapeutic intensity in patients with early BC since ET may significantly impact the quality of life for a



Number of patients at risk					
Months	0	36	60	84	120
No ET	1092	811	502	228	72
ET	4453	3117	2064	889	247

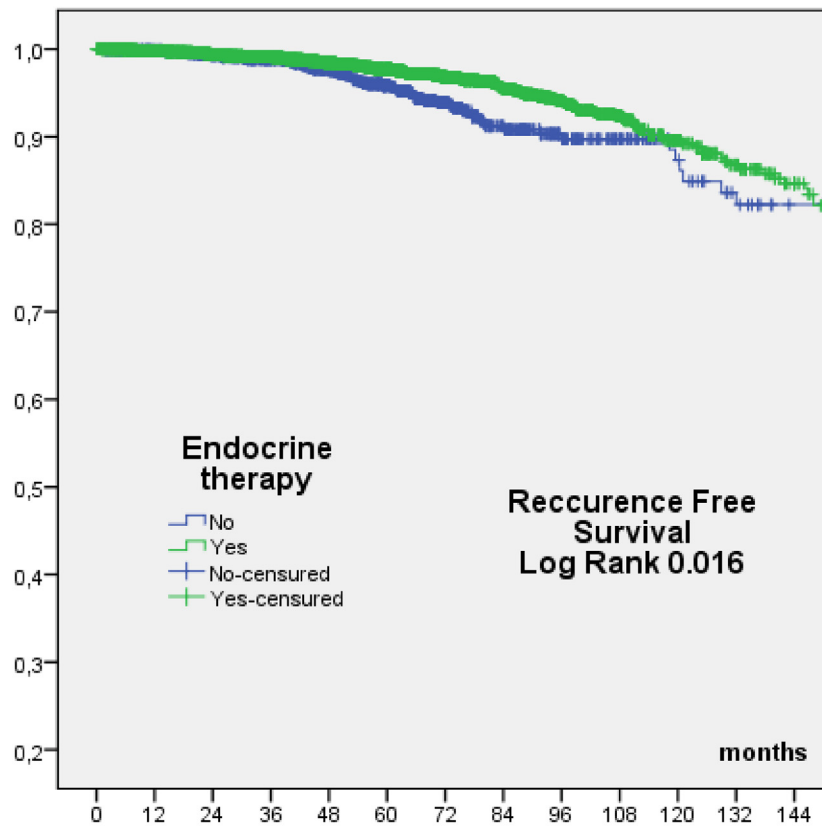
Fig. 2. Disease-free survival according to endocrine therapy (univariate analysis).

relatively small—though still significant—benefit, as indicated by our results in both our current and previous studies [14].

Our primary goal was to identify potential improvements due to ET in patients with ER-positive pT1a-b BC in order to expand current knowledge and aide clinicians in the decision-making for ET administration in these tumour types. We found that while there was significant improvement in both DFS and RFS and recurrences were less common in patients with ET, the absolute benefits were small, and OS was unaffected. Still, the results of our study were consistent with those of others. In the EBCTCG study of patients with early-stage ER-positive BC and who received ET for 5 years, the risk of distant recurrence in T1N0 BC at 10 and 15 years was 3% and 7%, respectively, for 5527 pT1a-bN0 tumours and 4% and 9%, respectively, for 13,875 pT1cN0 tumours (HR: 0.67, $p < 0.001$). The risk of any breast cancer event was 6% and 13% for pT1a-bN0 tumours versus 7% and 14% for pT1cN0 tumours at 10 and 15 years, respectively (HR: 0.85, $p = 0.01$).⁽²⁾ Our

DFS rates of 95.7% and 91.8% at 5 and 7 years, respectively, closely resembled these data. It is also clear that in both studies, patients with pT1a-b ER-positive grade 1 disease do not experience a significant benefit from ET, and as such, ET could potentially be omitted in these patients and should be discussed in accordance with the patient’s co-morbidities and/or tolerance of ET (if such treatment had been started).

Another relevant setting in which omitting ET could be considered appropriate concerns patients with pN0 status. In our study, the multivariate analysis of patients with pN0-pN0(i+) disease did not reveal any significant association between ET and OS or DFS. In fact, in terms of pN status, only pN1macro disease had any significant association with survival. A similar result was found in the EBCTCG study, where patients with T1N1, T1N2, T2N1 and T2N2 BC, all saw a minimum risk of recurrence of 20%. However, recurrences after five years of follow-up are not rare, and the authors themselves concluded that after 5-years of treatment ‘even low-grade T1N0 disease carries an appreciable risk of



Number of patients at risk					
Months	0	36	60	84	120
No ET	1087	811	502	229	73
ET	4444	3122	2070	898	257

Fig. 3. Recurrence-free survival according to endocrine therapy (univariate analysis).

Table 3

Multivariate Cox regression analysis of disease-free survival in all patients and subgroup of patients with grade 2–3 tumours.

		All patients				Grade 2-3			
DFS		<i>p</i>	Hazard ratio	CI 95%		<i>p</i>	Hazard ratio	CI 95%	
				Inferior	Superior			Inferior	Superior
Endocrine Therapy	Yes		1				1		
	No	0.047	1.275	1.003	1.620	0.049	1.502	1.001	2.252
Grade	1		1				1		
	2	0.743	1.037	0.834	1.291		1		
	3	0.211	1.327	0.852	2.068	0.211	1.331	0.850	2.085
LVI	No		1				1		
	Yes	0.002	1.668	1.207	2.305	0.045	1.551	1.009	2.382
Age	≤40		1				1		
	40.1–50	0.278	0.786	0.508	1.214	0.246	0.718	0.411	1.256
	50.1–74.9	0.298	0.812	0.548	1.202	0.080	0.641	0.389	1.055
	≥75	<0.0001	2.518	1.575	4.025	0.052	1.890	0.995	3.589
pN status	pN0		1				1		
	pN (i+)	0.170	1.483	0.844	2.606	0.023	2.150	1.111	4.161
	pN1mi	0.817	0.953	0.632	1.436	0.825	1.070	0.590	1.940
	pN1 macro	0.052	1.346	0.997	1.818	0.094	1.424	0.942	2.152
HER2	Unknown versus < 0	<0.0001	0.644	0.514	0.805	<0.0001	0.517	0.359	0.745
Surgery	Conservative		1				1		
	Mastectomy	0.947	1.010	0.746	1.368	0.925	0.980	0.640	1.499

Abbreviations: LVI, lymphovascular invasion.

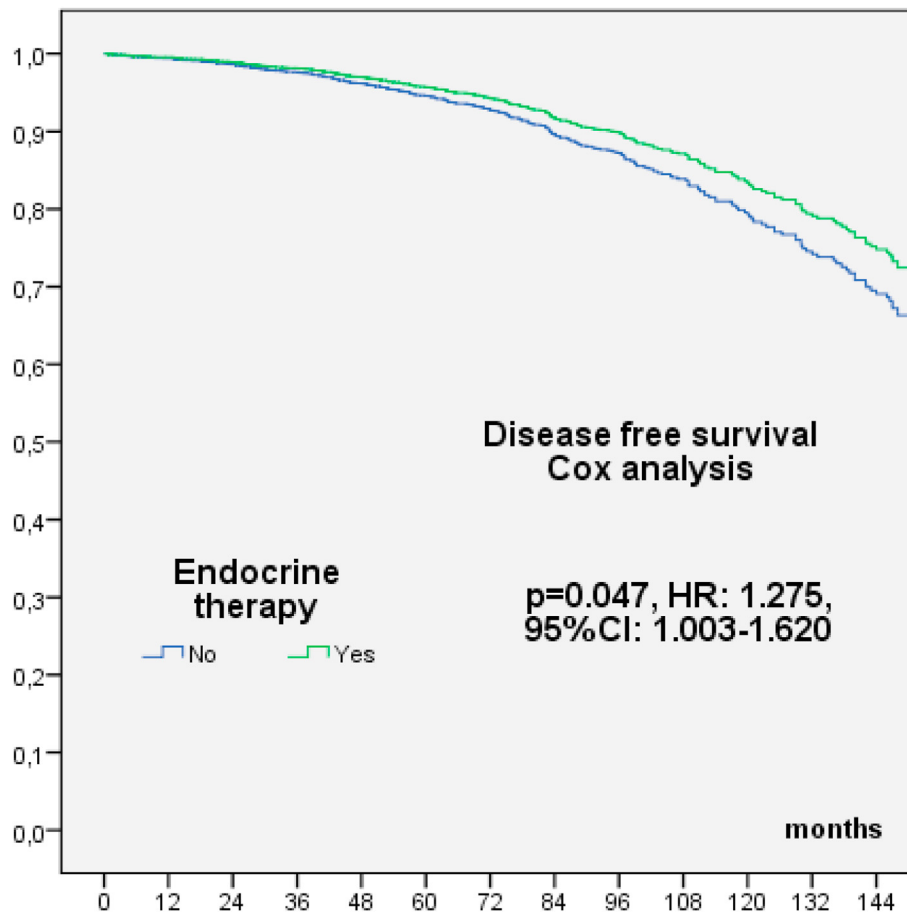


Fig. 4. Disease-free survival according to endocrine therapy for all patients in multivariate analysis.

distant recurrence and contralateral breast cancer, a risk that is sufficient for at least the consideration of extended ET[2].

Concerning intraoperative radiotherapy itself increased local recurrence has been observed in the absence of

hormone therapy [15,16]. In the TARGIT-A trial, the omission of whole-breast radiotherapy compared to intraoperative radiotherapy corresponded with an absolute increase in the local recurrence rate of approximately 7% at 5 years and 8% at 10 years, without any detectable

Table 4

Multivariate Cox regression analysis of overall survival in all patients and subgroup of patients with grade 2–3 tumours.

OS		All patients				Grade 2-3			
		p	Hazard ratio	CI 95%		p	Hazard ratio	CI 95%	
				Inferior	Superior			Inferior	Superior
Endocrine Therapy	Yes		1				1		
	No	0.349	1.179	0.835	1.663	0.272	1.361	0.785	2.360
Grade	1		1				1		
	2	0.837	0.966	0.697	1.339				
	3	0.011	2.009	1.174	3.440	0.008	2.122	1.217	3.699
LVI	No		1				1		
	Yes	0.241	1.359	0.813	2.272	0.375	1.363	0.688	2.704
Age	≤40		1				1		
	40.1–50	0.649	1.224	0.513	2.921	0.877	1.089	0.366	3.239
	50.1–74.9	0.062	2.120	0.964	4.662	0.153	2.016	0.770	5.277
	≥75	<0.0001	10.42	4.495	24.14	<0.0001	7.989	2.746	23.25
pN status	pN0		1				1		
	pN (i+)	0.985	1.010	0.370	2.757	0.274	1.781	0.633	5.014
	pN1mi	0.831	1.068	0.585	1.950	0.388	0.595	0.183	1.936
	pN1 macro	0.016	1.686	1.104	2.576	0.059	1.718	0.979	3.015

Abbreviations: LVI, lymphovascular invasion.

Table 5
Multivariate Cox regression analysis of recurrence-free survival in all patients and subgroup of patients with grade 2–3 tumours.

RFS		All patients				Grade 2-3			
		p	Hazard ratio	CI 95%		P	Hazard ratio	CI 95%	
				Inferior	Superior			Inferior	Superior
Endocrine Therapy	Yes		1				1		
	No	0.093	1.306	0.957	1.782	0.251	1.330	0.817	2.164
Grade	1		1				1		
	2	0.076	1.302	0.973	1.742		1		
	3	0.088	1.617	0.931	2.810	0.388	1.276	0.734	2.220
LVI	No		1				1		
	Yes	0.006	1.760	1.176	2.635	0.112	1.541	0.905	2.626
Age	≤40		1				1		
	40.1–50	0.304	0.769	0.465	1.269	0.822	0.929	0.489	1.764
	50.1–74.9	0.012	0.547	0.343	0.873	0.057	0.557	0.305	1.018
	≥75	0.505	0.787	0.389	1.592	0.483	0.689	0.244	1.950
pN status	pN0		1				1		
	pN (i+)	0.127	1.669	0.865	3.218	0.090	2.004	0.896	4.481
	pN1mi	0.979	1.007	0.586	1.731	0.696	1.154	0.564	2.360
	pN1 macro	0.284	1.245	0.834	1.859	0.600	1.151	0.680	1.950
Surgery	Conservative		1				1		
	Mastectomy	0.672	1.088	0.737	1.606	0.674	1.118	0.666	1.876
pT size	pT1a		1				1		
	pT1b	0.002	0.624	0.460	0.847	0.005	0.527	0.338	0.822

Abbreviations: LVI, lymphovascular invasion.

increase in breast cancer mortality [17]. Consequently, ET should be recommended for patients who have received only partial-breast irradiation, such as intraoperative radiotherapy, and the omission of ET should be likewise discouraged in patients benefiting from strategies of therapeutic de-escalation which have been validated in the context of ET.

Our study has several limitations. Concerning ER status, tumours were considered as ER-positive only

when 10% or more of cells stained positive. However, some patients have between 1% and 10% of cells staining positive [18,19], which may be considered as ER-positive according to US guidelines and thus allow for adjuvant endocrine treatment, but were not included in our study. Yet accumulating evidence demonstrates that their prognosis is quite similar to patients with ER-negative BC and with limited benefit from adjuvant ET [20–23]. In addition, due to the length of our inclusion period,

Table 6
Multivariate Cox regression analysis of OS, DFS and RFS in patients with HER2-negative tumours.

HER2 negative patients		OS				DFS				RFS			
		p	Hazard ratio	CI 95%		p	Hazard ratio	CI 95%		p	Hazard Ratio	CI 95%	
				Inf	Sup			Inf	Sup			Inf	Sup
Endocrine Therapy	Yes		1			1				1			
	No	0.157	1.386	0.882	2.176	0.267	1.200	0.870	1.655	0.964	1.010	0.650	1.569
Grade	1		1			1				1			
	2	0.928	1.019	0.679	1.529	0.475	1.105	0.840	1.455	0.232	1.252	0.866	1.810
	3	0.004	2.782	1.394	5.553	0.030	1.883	1.065	3.329	0.031	2.214	1.077	4.554
LVI	No		1			1				1			
	Yes	0.318	1.394	0.726	2.678	0.008	1.756	1.160	2.658	0.020	1.844	1.103	3.083
Age	≤40		1			1				1			
	40.1–50	0.244	3.357	0.437	25.77	0.952	0.979	0.499	1.922	0.512	1.314	0.581	2.971
	50.1–74.9	0.095	5.394	0.748	38.92	0.926	0.971	0.519	1.815	0.926	0.964	0.444	2.093
	≥75	0.002	23.86	3.207	177.5	0.003	2.905	1.449	5.827	0.444	1.466	0.550	3.905
pN status	pN0		1			1				1			
	pN (i+)	0.449	1.487	0.533	4.148	0.011	2.168	1.194	3.939	0.020	2.347	1.142	4.824
	pN1mi	0.819	0.899	0.360	2.241	0.363	0.751	0.405	1.392	0.595	0.810	0.372	1.763
	pN1 macro	0.107	1.621	0.901	2.916	0.841	1.046	0.675	1.621	0.928	0.974	0.555	1.712
Surgery	Conservative		1			1				1			
	Mastectomy					0.535	0.875	0.573	1.336	0.665	1.118	0.676	1.848
pT size	pT1a									1			
	pT1b									0.260	0.799	0.540	1.181

Abbreviations: LVI, lymphovascular invasion.

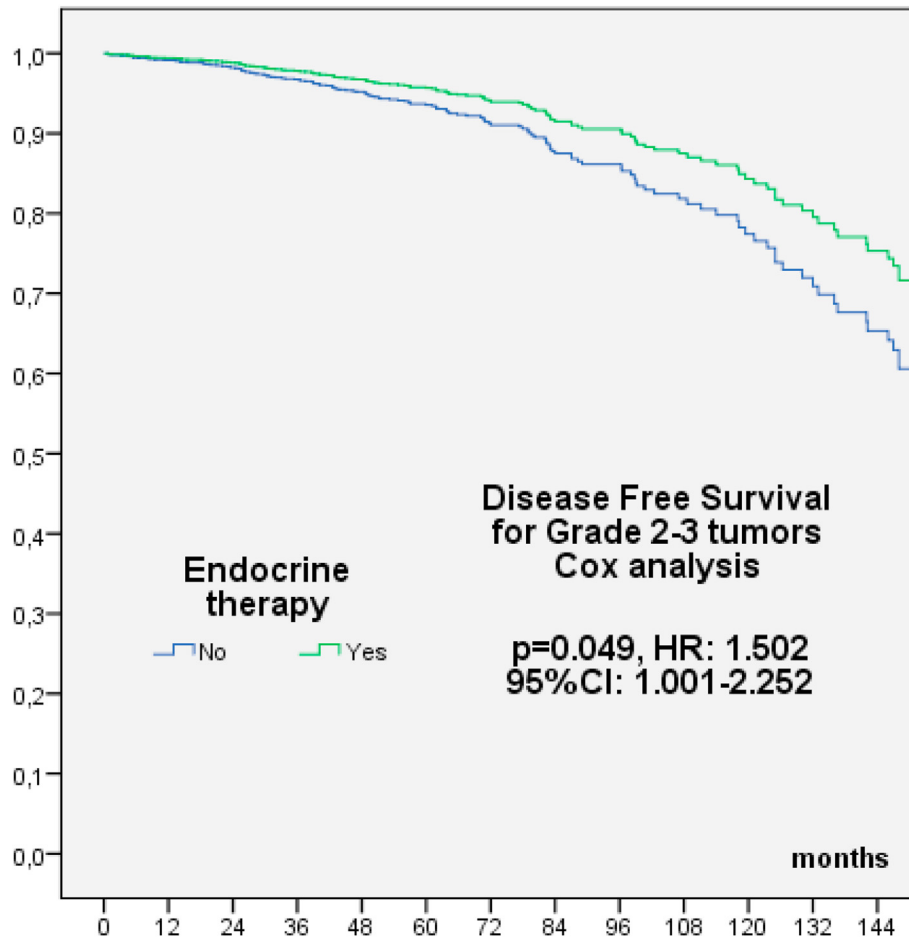


Fig. 5. Disease-free survival according to endocrine therapy for patients with grade 2–3 tumours in multivariate analysis.

1546 patients lacked analysis of HER2 status. The follow-up in our study was also relatively short and while only a small benefit was seen, the absolute difference between patients with or without ET could

actually be higher after 10 or 15 years of follow-up. Furthermore, our study lacked information concerning compliance with ET, as only a limited amount of data were detailed enough to include adherence. In addition,

Table 7

Overall survival, disease-free survival and recurrence-free survival multivariate Cox analysis in patients with pN0 or pN0(i+) axillary lymph nodes.

pN0 & pN0(i+)	OS				DFS				RFS			
	p	Hazard ratio	CI 95%		p	Hazard ratio	CI 95%		p	Hazard ratio	CI 95%	
			Inf	Sup			Inf	Sup			Inferior	Superior
Endocrine Therapy	Yes	1			1				1			
	No	0.318	1.210	0.833 1.758	0.348	1.188	0.829 1.703	0.082	1.363	0.961	1.933	
Grade	1	1			1			1				
	2	0.725	1.067	0.742 1.535	0.721	1.062	0.763 1.478	0.066	1.360	0.979	1.888	
	3	0.051	2.089	0.997 4.380	0.025	2.156	1.104 4.213	0.067	1.940	0.956	3.938	
LVI	Yes versus No	0.871	1.062	0.512 2.202	0.584	1.191	0.637 2.227	0.052	1.663	0.996	2.777	
Age	≤40	1			1			1				
	40.1–50	0.549	1.591	0.348 7.281	0.801	0.877	0.317 2.428	0.536	0.817	0.432	1.547	
	50.1–74.9	0.057	3.933	0.958 16.15	0.267	1.675	0.674 4.165	0.109	0.617	0.342	1.114	
	≥75	<0.0001	17.86	4.212 75.72	<0.0001	6.708	2.587 17.39	0.402	0.698	0.301	1.618	
pN status	pN (i+) versus pN0	0.913	1.058	0.386 2.895	0.859	1.085	0.441 2.670	0.113	1.710	0.880	3.320	
Her2	Unknown versus < 0				0.001	0.536	0.376 0.765	0.043	0.706	0.504	0.989	
Surgery	Mastectomy versus BCS				0.766	0.923	0.542 1.569	0.811	1.059	0.660	1.701	
pT1b vs pT1a								0.013	0.649	0.461	0.913	

Abbreviations: LVI, lymphovascular invasion; BCS, breast-conserving surgery.

due to the retrospective design of the study, we lacked stratification according to the menopausal status and the type of ET. The survival rates of patients who had not fully completed the therapy would therefore be somewhat lower than those in our study. On the other hand, one potential benefit of a shorter follow-up is that only a few of the patients received a BC diagnosis before the year 2000, which somewhat limits differences in treatments due to technological advances and changes to existing guidelines. Our study also benefitted from a high percentage (90.4%) of patients that underwent Sentinel lymph node biopsies and thus had a more extensive analysis of axillary lymph nodes than in older studies where axillary lymph node status was instead determined by axillary dissection. With over 5000 patients included in the study across 15 different centres, our results also carry greater statistical power than those of smaller studies, though—as noted previously—the administration of ET differed significantly between centres, and this could have affected the results.

5. Conclusions

In our study, adjuvant ET was significantly associated with a survival benefit in all patients with pT1a-bN0 ER-positive BC and particularly in those with grade 2–3 tumours, even with a relatively short follow-up for these patients who can recur even after 20–25 years and little data concerning compliance. However, the lack of consensus on ET administration resulted in largely different rates of ET for pT1a-b ER-positive BC across the various centres, and additional studies are needed to determine potential effects on survival in these patients. In addition, there was no beneficial impact of ET on survival in patients with pT1a-b ER-positive grade 1 BC, and as such, ET should be discussed—particularly for pT1a tumours—according to these patient’s co-morbidities and/or tolerance (if ET had already been started).

Author statement

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Appendix A. Supplementary data

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