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CLINICAL TRIAL

Isolated ipsilateral local recurrence of breast cancer: predictive factors and prognostic impact

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Abstract

Background Tumour features associated with isolated invasive breast cancer (BC) ipsilateral local recurrence (ILR) after breast conservative treatment (BCT) and consequences on overall survival (OS) are still debated. Our objective was to investigate these points.

Methods Patients were retrospectively identified from a cohort of patients who underwent BCT for invasive BC in 16 cancer centres. End-points were ILR rate and OS. The impact of ILR on OS was assessed by multivariate analysis (MVA) for all patients and according to endocrine receptors (ERs) and grade or tumour subtypes.

Results Of 15,570 patients, ILR rate was 3.1%. Cumulative ILR rates differed according to ERs/grade (ERs+/Grade2: HR 1.42, $p=0.010$; ERs+/Grade3: HR 1.41, $p=0.067$; ERs−: HR 2.14, $p<0.0001$), endocrine therapy (HR 2.05, $p<0.0001$) and age < 40-years old (HR 2.28, $p=0.005$) in MVA. When MVA was adjusted on tumour subtype, the latter was the only independent factor. OS-after-ILR was significantly different according to ILR-free intervals (HR 4.96 for ILR-free interval between 2 and 5-years and HR 9.00 when < 2-years, in comparison with ≥ 5-years).

Conclusion ERs/Grade status, lack of endocrine therapy and tumour subtypes predict isolated ILR risk in patients treated with BCT. Short ILR-free-intervals represent a strong pejorative factor for OS. These results may help selecting initial treatment as well as tailoring ILR systemic chemotherapy.

Keywords Ipsilateral · Local recurrence · Breast cancer · Survival · Prognosis

Abbreviations

ALND	Axillary LN dissection
BC	Breast cancer
BCT	Breast conservative treatment
CI	Confidence interval
ERs	Endocrine receptors
HER2	Human epidermal growth factor 2
HR	Hazard ratio
IHC	Immunohistochemistry
ILR	Ipsilateral local recurrence
ILRFS	Ipsilateral local recurrence-free survival
LN	Lymph node
LVI	Lympho-vascular invasion
OS	Overall survival
pN	Pathological node status
RNI	Regional nodal irradiation
SLNB	Sentinel lymph node biopsy
TNBC	Triple negative breast cancer

Introduction

The oncological outcomes of early breast cancer (BC) patients undergoing breast conservative treatment (BCT) or mastectomy are reported as equivalent [1–4]. Ipsilateral local recurrence (ILR) is a rare event with an estimated rate of 0.5–1.5% per year after BCT for invasive carcinoma and

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an overall incidence ranging from 5 to 10% after 10-years follow-up [1, 2, 5–7]. These incidences include all ILR, including ILR after or concomitant to another recurrence such as metastasis and/or axillary lymph node recurrence and/or contralateral breast recurrence. Few studies have analysed isolated ILR rates and their prognostic impact, with limited statistical power due to small sample size [8, 9]. Numerous predictive factors of ILR have already been identified but each time with strong interactions. Moreover, the impact of isolated ILR on overall survival remains discussed [10, 11]. These data could be of particular interest for patient/physician shared decision on selecting between BCT and mastectomy with or without immediate reconstruction at the initial phase of treatment, as well as tailoring ILR systemic therapies and second breast surgery.

The aim of our study was to examine predictive factors of isolated ILR after BCT with in sano resection and whole breast irradiation as well as the impact of such an ILR on overall survival in a large multi-institutional cohort.

Patients and methods

Study design and data source

We conducted a retrospective analysis of 20,676 BC patients treated between 1980 and 2013 in 16 French BC units. Consent for participating to the study and for personal data management was obtained from all patients. Patients and tumours characteristics, treatments, death and recurrences if any were retrieved from medical files. Patients were considered eligible if they had histologically proven invasive BC, underwent BCT with sentinel lymph node biopsy (SLNB) and/or axillary LN dissection (ALND), and had not received neoadjuvant chemotherapy. Only patients with in sano resection were included (without any ink on resection margin; (precision about close or large margins in millimetres was not available)). All patients received whole breast irradiation (at a median time of 6 weeks after surgery, or after adjuvant chemotherapy completion). Endocrine receptors (ERs: oestrogen receptor and/or progesterone receptor) were considered as positive if they were expressed in $\geq 10\%$ of the tumour specimen. HER2 status was determined by immunohistochemistry +/− fluorescent in situ hybridization [12]. Since HER2 testing was very uncommon until 2003, a first analysis adjusted to ER/Grade to recruit all patients was planned. BCs were then classified in five immunohistochemical sub-types as previously described [13] for cases with available HER2 status: Luminal-A (ER-positive/HER2-negative/grade 1–2), HER2-negative Luminal-B (ER-positive/HER2-negative/grade-3), HER2-positive Luminal-B (ER-positive/HER2-positive/all grades), HER2-positive (non-luminal, HER2-positive/ER-negative) and triple negative (TNBC: ER-negative/HER2-negative). To assess the biological heterogeneity of ERs-positive tumours, we further subdivided them in luminal-A grade-1 and luminal-A grade-2.

Statistical analysis

Categorical variables were described using counts and frequencies and quantitative variables were described using medians and ranges. Patients' characteristics were compared with χ^2. Isolated ILR was defined as invasive carcinoma recurrence in the skin or parenchyma of ipsilateral breast without any evidence of distant disease [14]. Only ILR as the first event occurring after surgery was considered. Others sites, including axillary LN recurrence and contralateral BC, were considered as other recurrence. If ILR and metastatic relapse occurred simultaneously, relapse was then considered as metastatic. ILR-Free-Survival (ILR-FS) was defined as the time from surgery to ILR. ILR-FS was categorised in three time intervals: ILR before 2 years of follow-up, between 2 and 5 years, and during or after the fifth years. Overall survival (OS) was defined as the time from surgery to death.

Known recurrence risk factors were analysed in univariate analysis: age, tumour size, lympho-vascular invasion (LVI), grade, pathological node status (pN), ERs status, tumour subtype and systemic therapies. The impact of ILR on OS was assessed through multivariate analysis by logistic regression and Cox model, adjusted on ERs/Grade status (ERs+/Grade 1, ERs+/Grade 2, ERs+/Grade 3 and ERs−) and then on tumour subtypes. Survival curves were generated using the Kaplan–Meier method and compared using the Log-rank test. The level of statistical significance was set at $\alpha = 0.05$. Statistical analyses were carried out with SPSS® software version 16.0. We followed the reporting recommendations specified in the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Statement [15].

Results

Patient characteristics

Of 20,676 patients of the overall cohort, 15,570 met the previously defined criteria. Baseline characteristics of the analysed population and ILR occurrences are reported in Table 1. SLNB was performed in 77.5% of patients (12,067) with complementary ALND for 32.9% of patients (3955/12,032). Patient's characteristics according to ERs/grade status and tumour subtypes are reported in Supplementary Tables 1 and 2. A large majority of ER-positive BC patients received endocrine therapy (88.5%; 11,420/12,911)

Table 1 Baseline characteristics of the analysed population and ILR occurrences

	Total population		ILR			ILRFS
	Nb	%	Nb ILR	% ILR	*p*	*p* (log rank)
Population	15,570		481	3.1		
Histology						
Ductal	12,429	79.8	405	3.3	0.033	0.076
Lobular	1879	12.1	51	2.7		
Mixed	213	1.4	7	3.3		
Others	1049	6.7	18	1.7		
Age (years)						
≤40	1000	6.4	76	7.6	< 0.0001	< 0.0001
41–50	3411	21.9	140	4.1		
51–75	10,106	64.9	250	2.5		
≥ 75	1051	6.8	15	1.4		
Unknown	2					
Grade						
1	5516	35.4	123	2.2	< 0.0001	< 0.0001
2	6935	44.5	229	3.3		
3	2744	17.6	98	3.6		
Unknown	375	2.5	31	8.3		
LVI						
Yes	3123	23.1	136	4.4	< 0.0001	0.006
No	10,390	76.9	262	2.5		
Unknown	2057					
Chemotherapy						
No	9880	63.5	294	3.0	0.426	0.090
Yes	5675	36.4	187	3.3		
Unknown	15	0.1	0			
Endocrine therapy						
No	3968	25.5	256	6.5	< 0.0001	< 0.0001
Yes	11,586	74.5	224	1.9		
Unknown	36					
ALN status						
Negative	10,956	70.4	329	3.0	0.002	0.272
i+	480	3.1	16	3.3		
mic	1134	7.3	19	1.7		
macro	3000	19.3	117	3.9		
ERs						
Negative	2633	16.9	182	6.9	< 0.0001	< 0.0001
Positive	12,937	83.1	299	2.3		
Luminal A						
Her2− RH+ G 1–2	7238	75.3	118	1.6	< 0.0001	< 0.0001
Her2+						
RH−	250	2.6	11	4.4		
Triple negative	845	8.6	35	4.1		
Luminal B						
Her2− RH+G3	790	8.2	18	2.3		
Luminal B						
Her2+RH+	486	5.1	10	2.1		
Tumour size						
≤ 5 mm	1052	6.8	41	3.9	0.006	0.057
5.1–10	4570	29.7	121	2.6		

Table 1 (continued)

	Total population		ILR			ILRFS
	Nb	%	Nb ILR	% ILR	*p*	*p* (log rank)
10.1–19.9	5912	38.4	167	2.8		
20–50	3747	24.3	137	3.7		
> 50	132	0.9	8	6.1		
Unknown	157					
RNI						
No	8771	63.8	218	2.5	< 0.0001	0.287
Yes	4975	36.2	207	4.2		
Unknown	1824					
Tumour location						
External	9298	59.7	290	3.1	< 0.0001	< 0.0001
Internal	4165	26.8	164	3.9		
Unknown	2107	13.5	27	1.3		

ERs endocrine receptors, *LVI* lympho-vascular invasion, *ALN* axillary lymph node, *RNI* regional nodal irradiation

and 36.4% of all patients received adjuvant chemotherapy. Among 650 HER2-positive BC patients, 377 (58%) received trastuzumab.

Predictive factors for ILR and ILR-free survival

At a median follow-up of 60.3 months (95% CI 65.7–67.1; mean: 66.4 months), the crude rate of ILR was 3.1% (481/15,570). Median ILR-FS was 64.0 months (95% CI 73.7–84.5) with 13.9% of ILR ($n = 64$) occurring during the two first years of follow-up, 33.4% ($n = 154$) between two and five years of follow-up and 52.7% ($n = 243$) during or after the fifth year. Distribution of ILR-FS (< 2, 2 to < 5, ≥5 years) was significantly different according to ER status ($p = 0.035$) and tumour subtypes ($p = 0.011$). Median ILR-FS were 53.2 months (95% CI 69.3–88.4) for ERs-negative patients and 68.5 months (95% CI 72.8–85.7) for ERs-positive. Regarding tumour subtypes, median ILR-FS were 62.1 months (95% CI 54.6–91.9) in Luminal-A grade-1 patients, 63.7 (95% CI 58.7–81.8) in Luminal-A grade-2, 28.6 (95% CI 22.9–46.1) in Her2-positive, 50.9 (95% CI 45.1–74.9) in TNBC, 34.2 (95% CI 22.8–55.9) in Luminal-B Her2-negative and 34.5 (95% CI 19.9–65.6) in Luminal-B Her2-positive (Supplementary Fig. 1). Of note, among 15,089 patients without ILR, we observed 1011 metastatic and 90 axillary recurrences as first event with respective median interval-times from initial surgery of 37.5 (95% CI 48–53) and 53.1 months (95% CI 54–71).

In univariate analysis, factors significantly associated with ILR-FS were grade, LVI, endocrine therapy, ERs, tumour size, age, tumour location and tumour subtypes. In multivariate analysis, independent factors for ILR-FS were grade 2, endocrine therapy and age ≤ 40-years old (Table 2). ILR-FS was analysed according to ERs status and grade (Supplementary Table 1). Cumulative ILR rates were significantly different according to ERs/grade status (ERs+/Grade 2: HR 1.428, 95% CI 1.09–1.87, $p = 0.010$; ERs+/Grade 3: HR 1.419, 95% CI 0.97–2.06, $p = 0.067$; ERs−: HR 2.143, 95% CI 1.62–2.83, $p < 0.0001$) and age < 40-years old (HR 2.284, 95% CI 1.28–4.08, $p = 0.005$) (Fig. 1a) with significant different interval-times of ILR according to ERs/grade. When adjusted on LVI, age and pN status, cumulative ILR rates were significantly different in ERs-positive/Grade 1 and ERs-positive/Grade 3 patients for those without endocrine therapy only (HR 1.958, 95% CI 1.19–3.22; $p = 0.008$ and HR 4.108, 95% CI 1.80–9.37; $p = 0.001$, respectively). Among ERs-positive/Grade 2 patients, cumulative ILR rates were significantly different for patients without endocrine therapy (HR 2.223, 95% CI 1.44–3.43; $p < 0.0001$) and ≤ 40-years old (HR 11.67, 95% CI 1.55–87.5; $p = 0.017$). Regarding ERs-negative tumours, only age independently impacted cumulative ILR rates (HR 0.376, 95% CI 0.17–0.82; $p = 0.014$ for 41 to 50-years old patients and HR 0.357, 95% CI 0.17–0.75; $p = 0.007$ for 51 to 74.9-years old patients). When multivariate analysis was adjusted on tumour subtypes, independent factors significantly associated with ILR were tumour subtypes Luminal-A grade 2, TNBC, Luminal-B Her2− and Her2+ in comparison with Luminal-A grade 1 (Table 2; Fig. 1b).

Impact of ILR on Overall Survival

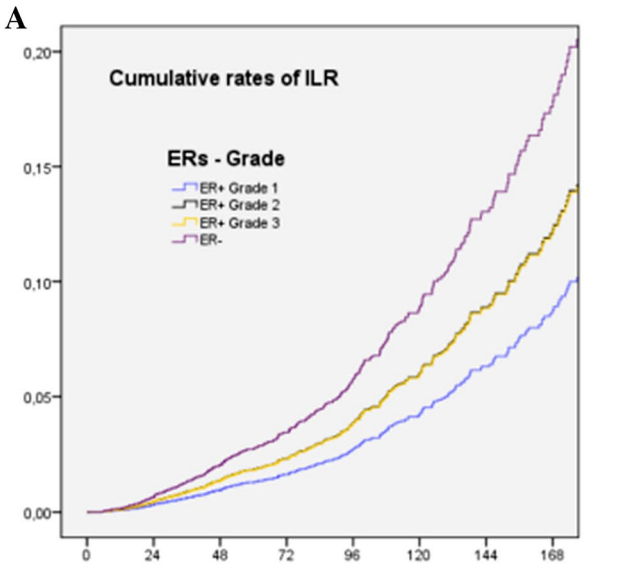
Factors significantly associated with OS in univariate analysis were age, grade, LVI, histologic type, adjuvant chemotherapy, endocrine therapy, ERs, tumour size, age, pN status, regional nodal irradiation, tumour subtypes and ILR. In multivariate analysis adjusted on ERs/Grade, ILR did not pejoratively impacted OS anymore (Table 3). When multivariate

Table 2 ILR-free survival: Cox regression analysis

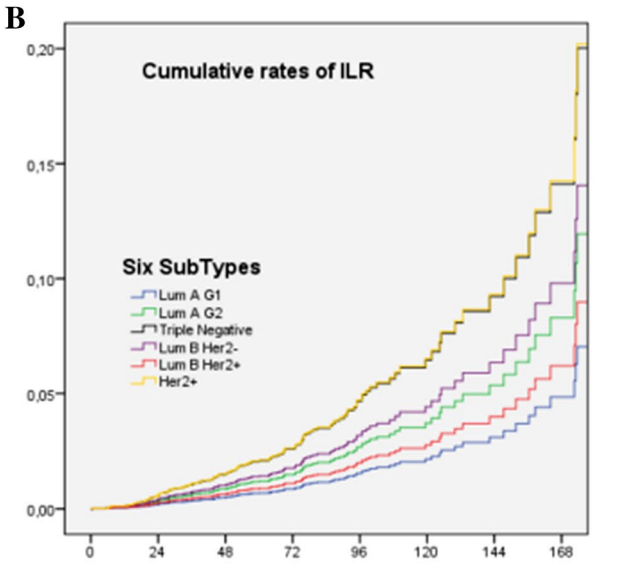
	Adjusted for ER				Adjusted for subtypes			
	p	HR	95% CI Inf	Sup	*p*	HR	95% CI Inf	Sup
Grade	1			1				
2	0.017	1.361	1.058	1.753				
3	0.102	1.31	0.948	1.811				
LVI								
No		1				1		
Yes	0.115	1.196	0.957	1.494	0.193	1.277	0.883	1.845
Endocrine therapy								
Yes		1						
No	< 0.0001	2.056	1.539	2.748				
ERs								
Positive		1						
Negative	0.85	0.97	0.709	1.328				
Tumour size								
≤ 5 mm		1				1		
5.1–10	0.847	0.955	0.598	1.525	0.825	0.904	0.37	2.206
10.1–19.9	0.951	0.986	0.622	1.561	0.998	0.999	0.426	2.342
20–50	0.605	0.883	0.551	1.414	0.884	0.937	0.393	2.236
> 50	0.074	2.114	0.929	4.807	0.275	2.044	0.567	7.372
Age								
≥ 75		1				1		
≤ 40	0.025	1.955	1.086	3.52	0.147	1.827	0.81	4.122
41–50	0.705	1.115	0.634	1.96	0.993	1.004	0.464	2.173
51–75	0.868	0.955	0.554	1.646	0.393	0.727	0.349	1.512
Tumour location								
External		1				1		
Inner	0.181	1.156	0.935	1.428	0.9	1.023	0.717	1.461
Tumour subtypes								
Lum A G1						1		
Lum A G2					0.014	1.741	1.119	2.708
Triple negative					< 0.0001	3.059	1.812	5.164
Lum B ER−					0.024	2.073	1.102	3.901
Lum B ER+					0.575	1.289	0.531	3.126
Her2+					0.013	3.09	1.274	7.496

ERs endocrine receptors, *LVI* lymphovascular invasion

analysis was adjusted on tumour subtypes, factors independently associated with OS were tumour size, age, LVI, axillary LN macro metastases, tumour subtypes but still not ILR (Table 3). However, categorised ILR-free interval significantly impacted OS rates ($p < 0.0001$). In multivariate analysis, an ILR-free interval ≥ 5-years was independently associated with favourable OS (HR 0.139, 95% CI 0.059–0.326; $p < 0.0001$) in comparison with ILR-free interval < 2-years. OS rates were significantly different for patients without ILR and patients with different ILR-free intervals: HR 0.235 (95% CI 0.15–0.37; $p < 0.0001$) for ILR-free intervals > = 5-years, HR 1.307 (95% CI 0.91–1.88; $p = 0.148$) for ILR-free intervals between 2 and 5 years and HR 2.404 (95% CI 1.53–3.78; $p < 0.0001$) for ILR-free intervals < 2-years, in comparison with patients without ILR (Fig. 2a). When multivariate analysis was adjusted on ERs/Grade status, OS rates were significantly different for patients without ILR and patients with ILR-free interval < 2-years (HR 1.896, 95% CI 1.20–2.99; $p = 0.006$) and ≥ 5-years (HR 0.235, 95% CI 0.15–0.37; $p < 0.0001$) (Fig. 2b). When multivariate analysis was adjusted for tumour subtypes, OS rates were significantly different for patients without ILR and patients with ILR-free interval < 2-years or between 2 and 5 years and for different tumour subtypes (Supplementary Table 3, Fig. 2c). For Luminal-A tumours, OS rates were significantly different between patients without ILR and patients with ILR-free interval < 2-years (HR 5.203, 95% CI 1.67–16.2; $p = 0.005$) and between 2 and 5-years (HR 3.235, 95% CI



	Nb at risk	2-years	5-years	7-years	10-years
ER+ Grade 1	5146	4288	2503	1129	243
ER+ Grade 2	6033	4991	2741	1254	323
ER+ Grade 3	1549	1315	657	305	103
ER-	2467	2048	1229	793	423



	Nb at risk	2-years	5-years	7-years	10-years
Luminal A G1	3439	2733	1412	537	120
Luminal A G2	3753	2937	1334	473	104
Triple negative	845	687	333	167	61
Luminal B Her2-	790	642	245	84	22
Luminal B Her2+	486	408	217	85	21
Her2+	250	201	87	41	8

Fig. 1 Cumulative ILR-free survival rates: **a** all patients; **b** according to tumour subtypes

1.59–6.55; $p = 0.001$) (Fig. 2d). For tumour subtypes others than Luminal-A, OS rates were significantly different between patients without ILR and patients with ILR-free interval < 5-years (HR 1.893, 95% CI 1.10–3.26; $p = 0.021$) (Fig. 2e).

When considering overall survivals after ILR-events, survivals were significantly different according to ILR-free interval with HR 4.96 (95% CI 2.7–9.0) for ILR interval between 2-years and < 5-years, and HR 9.00 (95% CI 4.7–17.4) for ILR interval < 2-years in comparison with patients with ILR-free interval ≥ 5-years (Fig. 3).

Discussion

We reported significant different ILR rates and outcomes according to ERs/Grade and tumour subtypes in a large multi-institutional cohort. Few studies focused on isolated ILR, considering all local recurrence events (isolated ILR, but also concomitant ILR to another recurrence site). The incidence of ILR following BCT is estimated from 5 to 10% in studies with 10-years follow-up from the initial tumour treatment [1, 2, 5–7]. Several factors were reported with a significant predictive impact on LR rate, but strong interactions between these factors make multivariate analysis on large cohorts much more capable to determine independent parameters significantly associated with recurrences.

Several recent studies have suggested the role of tumour subtype in the risk of local recurrences following BCT with an increased risk in TNBC and HER2-positive cancers without HER2-directed therapy [16–22]. However, no significant differences between molecular subtypes were reported by other studies [23, 24]. Gene expression patterns of BC distinguish distinct molecular subtypes but these molecular signatures are costly, and less expensive immunohistochemistry (IHC) surrogates for major intrinsic biologic subtypes with different prognosis [23, 25–28]. In this paper, we used a previously described IHC-approximation of 5 tumour subtypes based on ERs, HER2 and grade, delineating luminal-A, luminal-B HER2−, luminal-B Her2+, TNBC and HER2+ tumours [13]. In addition, luminal-A tumours were further subdivided according to grade. Indeed, we believe that separating ERs-positive HER2-tumours in three groups, luminal-A grade 1, luminal-A grade 2 and luminal-B HER2− (ER+, HER2− and grade 3) might more effectively capture biological heterogeneity of these ERs-positive tumours. Interestingly, luminal-A grade 2 was associated with shorter ILR-FS compare to luminal-A grade 1.

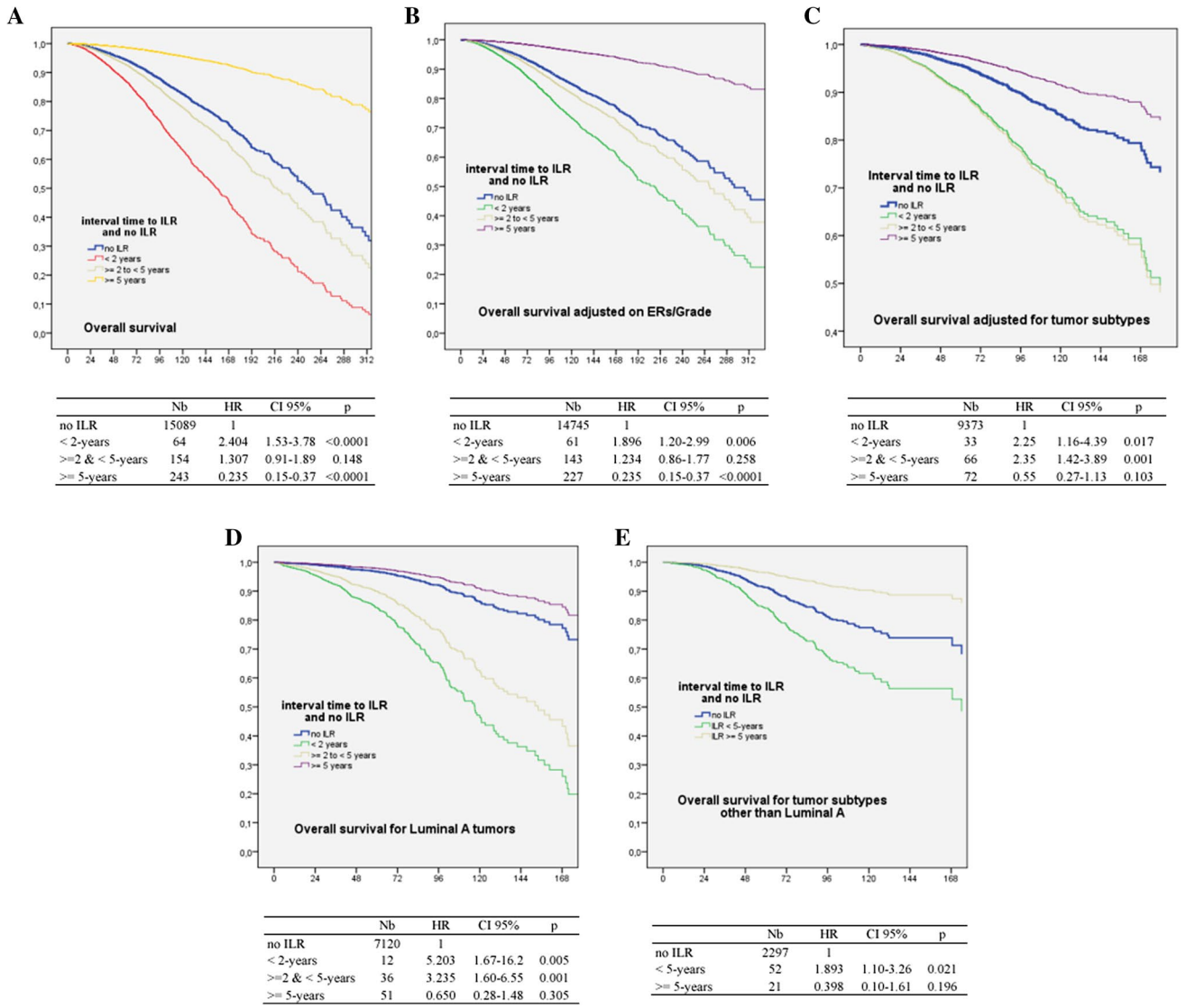
Braunstein et al. reported a multi-institutional cohort study of 2233 patients who underwent BCT, and found

Table 3 Impact of ILR on overall survival

	Adjusted for Ers/grade				Adjusted for tumour subtypes			
	p	HR	CI 95%		*p*	HR	CI 95%	
			Inferior	Superior			Inferior	Superior
Age								
≤40		1				1		
41–50	0.037	0.783	0.622	0.986	0.784	1.065	0.68	1.667
51–75	0.107	1.183	0.964	1.452	0.024	1.597	1.065	2.396
≥ 75	< 0.0001	3.231	2.471	4.224	< 0.0001	4.637	2.918	7.368
Histology								
Ductal		1				1		
Lobular	0.026	0.778	0.623	0.97	0.67	0.935	0.685	1.276
Mixt	0.328	0.781	0.475	1.282	0.523	0.783	0.369	1.661
Others	0.581	1.088	0.807	1.467	0.284	1.214	0.852	1.731
LVI								
Yes versus no	< 0.0001	1.404	1.23	1.603	0.039	1.257	1.012	1.561
Chemotherapy								
No		1				1		
Yes	< 0.0001	0.719	0.617	0.836	< 0.0001	0.577	0.452	0.735
Tumour size								
≤5 mm		1				1		
5.1–10	0.603	1.111	0.747	1.654	0.178	1.499	0.831	2.704
10.1–19.9	0.03	1.532	1.043	2.249	0.176	1.492	0.836	2.662
20–50	< 0.0001	2.431	1.655	3.571	0.001	2.615	1.463	4.674
> 50	< 0.0001	5.634	3.428	9.261	< 0.0001	5.899	2.877	12.096
ALN status								
pN0		1				1		
pN0 (i+)	0.261	0.772	0.492	1.212	0.555	0.832	0.452	1.532
pN1mi	0.202	0.809	0.584	1.12	0.523	0.879	0.591	1.307
pN1macro	< 0.0001	1.975	1.694	2.303	< 0.0001	1.913	1.509	2.426
ILR								
Yes versus no	0.002	0.659	0.508	0.854	0.123	1.35	0.922	1.977
ERs/grade								
ER+ grade 1		1						
ER+ grade 2	0.001	1.375	1.136	1.664				
ER+ grade 3	< 0.0001	2.45	1.961	3.06				
ER−	< 0.0001	1.695	1.345	2.136				
Endocrine therapy								
No versus yes	< 0.0001	2.007	1.652	2.44				
Tumour subtypes								
Lum A G1						1		
Lum A G2					0.025	1.344	1.039	1.739
Triple negative					< 0.0001	3.337	2.46	4.528
Lum B ER−					< 0.0001	2.896	2.11	3.974
Lum B ER+					0.002	2.03	1.297	3.178
Her2+					< 0.0001	2.904	1.723	4.895

ALN axillary lymph node, *ERs* endocrine receptors, *LVI* lymphovascular invasion

tumour subtypes, age ≤ 50-years old and involved axillary LN as predictive factors of ILR rates [9]. However, adjuvant therapies such as chemotherapy, endocrine therapy and regional nodal irradiation were different according to LN status. In our study with early BC patients, 19.3% of patients had involved LN macro metastases in comparison with 30% in Braunstein et al. study, LN status being correlated with tumour subtype [29]. In our study, multivariate analysis



	Nb	HR	CI 95%	p
no ILR	15089	1		
< 2-years	64	2.404	1.53-3.78	<0.0001
>=2 & < 5-years	154	1.307	0.91-1.89	0.148
>= 5-years	243	0.235	0.15-0.37	<0.0001

	Nb	HR	CI 95%	p
no ILR	14745	1		
< 2-years	61	1.896	1.20-2.99	0.006
>=2 & < 5-years	143	1.234	0.86-1.77	0.258
>= 5-years	227	0.235	0.15-0.37	<0.0001

	Nb	HR	CI 95%	p
no ILR	9373	1		
< 2-years	33	2.25	1.16-4.39	0.017
>=2 & < 5-years	66	2.35	1.42-3.89	0.001
>= 5-years	72	0.55	0.27-1.13	0.103

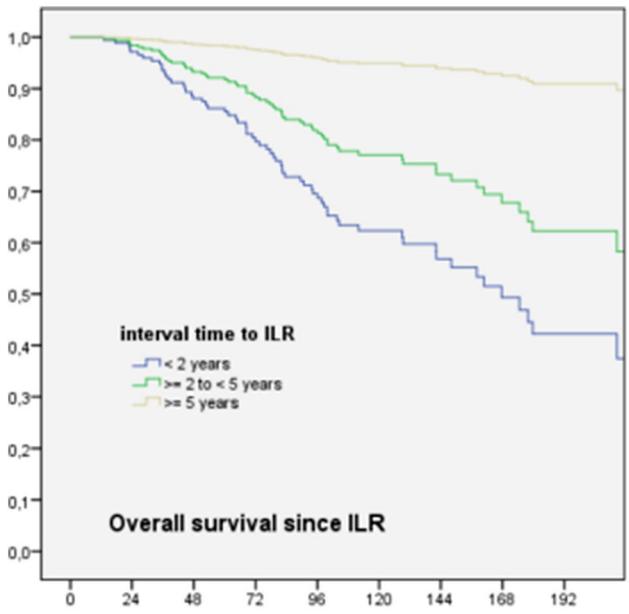
	Nb	HR	CI 95%	p
no ILR	7120	1		
< 2-years	12	5.203	1.67-16.2	0.005
>=2 & < 5-years	36	3.235	1.60-6.55	0.001
>= 5-years	51	0.650	0.28-1.48	0.305

	Nb	HR	CI 95%	p
no ILR	2297	1		
< 5-years	52	1.893	1.10-3.26	0.021
>= 5-years	21	0.398	0.10-1.61	0.196

Fig. 2 Impact of free interval-time on OS: **a** all patients; **b** adjusted for ERs/Grade status; **c** adjusted for tumour subtypes; **d** luminal-A tumours; **e** subtypes others than Luminal-A

showed that cumulative ILR rates were significantly different according to tumour subtypes only, underlying biologic correlations with others factors analysed. Braunstein et al. reported 8-years LR-risk of 1.8% for patients with luminal-A disease, 5.5% for luminal-B, 2.2% for luminal-HER2+, 11.7% for HER2+ and 9.8% for TNBC. Liu et al. [28] reported a 10-year estimates rates of 5.2% for Luminal-A tumours, 10.5% for Luminal-B tumours and 21.3% for others tumours considered as high risk. In Turashvili et al. study, among 2326 patients with BCT or mastectomy, 21-gene Recurrence-Score was predictive of loco-regional recurrence in lymph node-negative, ER-positive BC [30]. The other significant factor was T-stage. In addition, Mamounas et al. reported a significant prediction of loco-regional recurrence with 21-gene Recurrence-Score in node-positive, ER-positive BC patients after adjuvant chemotherapy associated with tamoxifen among 1065 patients treated by BCT or mastectomy included in NSABP B-28 trial [31].

Many empirical interval-time cut-off values were reported in literature (1, 2 or 5 years) [5, 32–39], and the magnitude of the prognostic impact of interval-time to ILR was reported with differences between patients with ERs-negative and ERs-positive tumours [8]. In our study, when OS was adjusted for tumour subtypes, OS rates were higher for interval-time ≥ 5-years without difference for intervals < 2-years or between 2 and 5-years. OS rates were higher for patients with ILR occurrence ≥ 5-years in comparison with patients without ILR, because 7.2% of these patients had metastatic or axillary recurrence which is a pejorative factor for oncological outcome [40]. Interestingly, the major unfavourable



Interval time	Nb	HR	CI 95%	p
>= 5-years	243	1		
< 2-years	64	9.006	4.67-17.4	<0.0001
>=2 & < 5-years	154	4.957	2.72-9.03	<0.0001

Fig. 3 Overall survival since ILR according to interval time of ILR

prognostic impact of short ILR-free interval was also demonstrated in Luminal-A tumours, which have been classically considered as more indolent subtypes. Short-time interval of ILR is more frequently observed in younger patients and in HER2+, Luminal-B and TNBC tumour subtypes, with in these cases a more unfavourable outcome. A short interval-time is a strong determinant of risk for distant metastasis [5, 7, 35, 38, 39] and poor prognosis [5, 32, 34–40]. These observations contribute to support more aggressive adjuvant therapy for these ILR with short interval-time and to propose distinct surveillance plan for patients with high risk of ILR.

The benefit of adjuvant chemotherapy for ILR was reported in a randomised trial [41] with HR of 0.59 ($p = 0.046$) in comparison with patients without chemotherapy, but only for ERs-negative in subgroup analysis. Yet, the impact of short interval-time on efficacy of adjuvant chemotherapy was not evaluated in this study. Of note, short interval-time of ILR is also considered as an unfavourable factor to propose a second conservative treatment of ILR [42].

Some limitations of the present study can be underline: our cohort was not prospective, without precision about close or large margins and we could not analyse family risk of BC as the presence of BRCA alteration. However, clear margin without ink on tumour specimen resection appears as sufficient quality resection for invasive BC [22, 43]. Also, our five-year median follow-up could be considered relatively short considering that patients with ER-positive breast cancer maintain a significant recurrence rate during extended follow-up [44]. Nevertheless, we succeed to find statistically significant differences through the large number of patients included in our cohort over an extended recruitment period.

In conclusion, breast cancer ERs/Grade status and molecular subtypes predict risk of ILR in early BC patients treated with BCT and short interval-time to ILR represent a strong pejorative factor for overall survival. These results may contribute to patients and physicians information and help them in initial surgical treatment selection as well as for deciding ILR adjuvant therapy and second breast conservative surgery.

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Compliance with ethical standards

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Informed consent All included patients provided written informed consent before surgery.

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