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Original Article

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Long-term outcome of isolated locoregional breast cancer recurrence: a large retrospective mono-institutional study

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Abstract

Background: **Isolated locoregional relapse (ILRR) after curative treatment for early breast cancer (BC) is associated with poor prognosis. Treatment strategies are poorly standardized. We aimed at exploring prognostic factors and long-term outcomes of ILRR.**

Patients and methods: **Overall, 1070 patients diagnosed with stage I-III BC between 2000 and 2007 were identified from a large mono-institutional dataset, with long follow up. Among these, 66 patients (6%) presented an ILRR as first BC event and 33% subsequently presented a distant recurrence (DR) (22/66).**

Results: **In the overall study cohort, patients with ILRR presented a significantly higher risk of DR compared to those without ILRR ($P < .001$). However, while being diagnosed with a DR was significantly associated with a worse overall survival (OS), ILRR was not. In the subgroup of patients with ILRR ($N = 66$), more advanced nodal status at initial diagnosis and HER2-positivity on the ILRR were significantly associated with worse distant relapse-free interval (DRFI) post-ILRR and worse OS post-ILRR. Moreover, switching from HR+ primary BC to HR− ILRR was associated with worse OS post-ILRR. In multivariate analyses, nodal involvement at primary diagnosis remained independently associated with both DRFI and OS post-ILRR, while HER2+ ILRR was independently associated with worse OS post-ILRR.**

Conclusion: **Patients diagnosed with ILRR after curative treatment for primary BC are at higher risk of subsequent DR, highlighting the need for prompt diagnosis and treatment of ILRR. Moreover, biological recharacterization of ILRR provides potential key prognostic and predictive factors, such as HR loss, allowing personalization of treatment and follow-up after ILRR.**

Key words: breast cancer, isolated locoregional relapse, clinical outcome, biological recharacterization

Implication for Practice

This study is a retrospective analysis involving a large dataset of patients diagnosed with stage I-III breast cancer (BC) between 2000 and 2007 at a single institution. Patients experiencing an invasive isolated locoregional recurrence (ILRR) have a substantial risk of subsequent distant metastases. Notably hormone (HR) receptor loss (HR+ primary BC converting to HR− ILRR), as well as developing an HER2+ ILRR, were negative prognostic factors for outcome. To date, treatment strategies for locally relapsing patients is poorly standardized. Our data support the need for re-evaluation of tumor biology at recurrence to guide treatment decisions and to personalize follow-up.

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Introduction

Advances in diagnosis, local and systemic management of stage I-III breast cancer (BC) have significantly improved disease control rates over time. However, in a significant number of cases, a locoregional recurrence (LRR; ie, ipsilateral tumor recurrence in the breast/chest wall or the regional lymph nodes) will occur after radical treatment of the primary disease.[1] Well-known clinical risk factors, such as larger tumor size, number of positive lymph nodes, hormone receptors (HR) negativity and human epidermal growth factor receptor 2 (HER2) positivity at diagnosis, have been reported to be associated with the risk of developing LRR.

Whenever possible, surgical removal of locally recurrent disease, with curative intent, should be pursued. Furthermore, as LRR is associated with a high risk of distant metastases and poor prognosis, the use of systemic therapy should also be taken into consideration.[2–5] Nevertheless, the evidence on adjuvant systemic therapy after radical resection of LRR is extremely limited. Indeed, to date, the results of two randomized trials exploring systemic treatment for patients with LRR after radical treatment of a primary BC have been reported. In the Swiss Group for Clinical Cancer Research (SAKK) 23/82 study, adjuvant tamoxifen significantly improved disease-free survival (DFS) compared with placebo in a population of 167 patients with HR-positive LRR treated with mastectomy.[6] In the CALOR (Chemotherapy as Adjuvant for Locally Recurrent Breast cancer) trial, which evaluated the use of adjuvant chemotherapy after radical resection of an isolated locoregional relapse, occurring in the breast, mastectomy scar/chest wall or lymph nodes, showed a significant improvement in DFS with the use of chemotherapy in BC patients with estrogen receptor (ER)-negative disease, while no effect was evident in those with ER-positive disease.[7] In this study, a statistically significant interaction between ER status of the local recurrence and benefit from chemotherapy was observed, thus highlighting the importance of reassessing the biological features of the disease to guide treatment choice. In a more contemporary treatment scenario, the ongoing POLAR trial is currently evaluating the potential benefit of the CDK4/6 inhibitor palbociclib given as adjuvant treatment for 3 years in combination with endocrine therapy in patients with radically resected HR-positive LRR.[8]

To explore the incidence and oncological outcomes of invasive isolated LRR (ILRR) in BC patients and to identify potential prognostic factors, we analyzed a large retrospective mono-institutional dataset.

Methods

Patient population and pathological assessment

We retrospectively examined the medical records of consecutive female patients who received upfront radical surgery for newly diagnosed primary stage I-III BC at our institution between 2000 and 2007. Patients undergoing neoadjuvant chemotherapy, with de novo metastatic disease or with a previous diagnosis of BC were excluded.

Histopathological assessments were conducted according to clinical practice on the surgical specimens. ER and PgR positivity were defined as nuclear staining of ≥1% of invasive tumor cells. HER2 was analyzed by immunohistochemistry as 0, 1+, 2+ or 3+ according to ASCO/CAP guidelines and, when indicated, by FISH. HER2 positivity was defined as HER2 3+ (immunohistochemistry) or 2+ and FISH amplified.

Definition of survival outcomes

ILRR was defined as isolated ipsilateral invasive tumor recurrence in the breast/chest wall or in the regional lymph nodes, after primary surgery for invasive BC.[17] In situ tumors were excluded. Moreover, in accordance with STEEP definition, ipsilateral invasive breast cancers were considered as a recurrence rather than a second primary BC.[17]

Recurrence in distant lymph nodes or other organs was classified as distant recurrence. Patients who experienced a distant recurrence within 3 months of ILRR were censored at the time of ILRR diagnosis for all analyses assessing ILRR. Furthermore, considering the competing risk, patients with distant failure before any other locoregional event were censored at time of distant metastases diagnosis for all analyses assessing ILRR.

ILRR-free interval was defined as the time interval from BC diagnosis to the first ILRR or last follow-up, whichever first.

Distant relapse-free interval was defined as the time interval from BC diagnosis to the occurrence of distant recurrence or last follow-up, whichever first.

DRFI post-ILRR was calculated, for patients experiencing an ILRR event, as the time interval from the first diagnosis of ILRR to distant recurrence or last follow-up, whichever first.

Overall survival (OS) was calculated from BC diagnosis to death from any cause or last follow-up, whichever first.

OS post-ILRR was calculated, for patients experiencing an ILRR event, as the time interval from the first diagnosis of ILRR to death from any cause or last follow-up, whichever first.

Statistical analysis

The impact of clinical-pathological features on outcomes in terms of HRs and the 95% CI was calculated by uni- and multivariate Cox regression model. An additional exploratory multivariable model was performed to assess the impact of chemotherapy administered at the time of ILRR, adjusting for selected key prognostic factors.

The Kaplan Meier method was used to perform survival analyses; comparisons between groups were assessed by the log-rank test. To address potential immortal time bias in the analysis of OS according to ILRR, additional analyses were performed using (i) a time-dependent Cox regression model including ILRR as a time-varying covariate, and (ii) a landmark analysis at 3 and 5 years from primary diagnosis.

All *P*-values were two-sided, with the significance level set at $P < .05$.

All analyses were carried out using IBM SPSS version 25.

Ethical considerations

The study was approved by the Institutional Review Board of Istituto Oncologico Veneto IOV IRCCS (CESC IOV 2019/48) and conducted according to the Declaration of Helsinki. Given the retrospective design, a specific informed consent was not required.

Results

Patients' characteristics at first BC diagnosis

We identified 1070 BC patients, diagnosed between 2000 and 2007, with available clinico-pathological and follow up data.

Patients' characteristics at first BC diagnosis are summarized in Table 1.

Median age was 55 years (range 46-66) and 64% ($N = 688$) were post-menopausal at the time of first BC diagnosis. Around 30% of patients ($N = 316$) had a tumor of more than 2 cm, and nodal involvement was present in 37% of patients ($N = 399$).

Most patients included in this analysis (90%, $N = 969$) presented with an HR+ tumor. As was expected considering the years of diagnosis, HER2 assessment was not available for around one third of cases (34%, $N = 366$). Among the 704 patients with known HER2 status, HER2 was positive (ie, IHC 3+ or IHC 2+ with amplification at subsequent FISH) in 18.5% of cases ($n = 130$).

Seventy percent of patients (70%, $N = 751$) were treated with breast-conserving surgery at first BC diagnosis. Overall, information regarding adjuvant systemic treatment was available for most patients ($N = 1060$ and $N = 1052$ had available information regarding adjuvant chemotherapy and endocrine therapy, respectively). Chemotherapy was given in 65% of cases ($N = 693$), mainly anthracycline-based for 51% of patients with available treatment data. As expected, among patients with HR+ BC, 86% ($N = 841$) received adjuvant endocrine therapy (tamoxifen, aromatase inhibitors or a sequence of both). Only 30 patients with HER2+ BC received trastuzumab (23%; 30/130), which was consistent with the regulatory approval of adjuvant trastuzumab in Italy.

Prognostic factors affecting ILRR-free interval

At a median follow-up of 177 months, a LRR was observed in 70 patients (6.5%; 70/1070). As a synchronous DR (ie, evidence of distant metastases within 3 months from the occurrence of LRR) was present in 4 cases, these patients were excluded from subsequent analyses, focused on the cohort of patients with BC with an ILRR (Figure 1).

Hence, the ILRR rate was 6% (66/1070). Median ILRR-free interval from the first BC diagnosis was 93 months (42-125 months).

At the univariate Cox regression model, no significant difference in ILRR-free interval according to clinicopathological features at diagnosis (menopause, T and N status, grade, HR and HER2 status) was observed (Supplementary Table S1). A numerical trend towards a lower risk of ILRR for patients receiving chemotherapy was observed (HR 0.63 95% CI 0.39-1.03; $P = .068$).

Clinical-pathological features of ILRR

Clinicopathological features of ILRR and type of treatment received by patients for ILRR are reported in Table 2.

When re-evaluated on the ILRR, ER and/or PgR were positive in 74% of cases ($N = 49$), while HER2 was overexpressed/amplified in 17% of cases ($n = 11$). Among patients initially diagnosed with an HR-positive primary BC ($N = 53$), loss of HR-positivity on the ILLR was observed in 7 patients (13%).

Tumor histological grade re-evaluated on the ILRR was only available for around half of cases ($N = 35$, 53%), all classified as grade 2 ($N = 19$, 54% of evaluable cases) or grade 3 ($N = 16$, 46% of evaluable cases).

Table 1. Patients' characteristics and treatment received at the first diagnosis of breast cancer (total $N = 1070$).

		N (%)
Age (median, range)	55 (46-66)	
Menopause	No	379 (35)
	Yes	688 (64)
	Missing	3 (1)
pT	1	744 (70)
	2	274 (25)
	3	22 (2)
	4	20 (2)
	Missing	10 (1)
pN	0	628 (59)
	1	299 (28)
	2	69 (6)
	3	31 (3)
	Missing	43 (4)
Grade	1/2	700 (65)
	3	289 (27)
	Missing	81 (8)
ER	Negative	159 (15)
	Positive	904 (84)
	Missing	7 (1)
PgR	Negative	151(14)
	Positive	907(85)
	Missing	12 (1)
HR	Negative	94 (9)
	Positive	969 (90)
	Missing	7 (1)
HER2 (IHC/FISH)	Negative	574 (54)
	Positive	130 (12)
	Missing	366 (34)
Breast Surgery Type	BCS	751 (70)
	Mastectomy	314 (29)
	Missing	5 (1)
ET[a]	No	123 (13)
	Yes	831 (86)
	Missing	15 (2)
CT	No	365 (34)
	Yes	693 (65)
	Missing	10 (1)
Trastuzumab[b]	No	67 (52)
	Yes	30 (23)
	Missing	33 (25)

Abbreviations: *N*, number; ER, estrogen receptor; PgR, progesterone receptor; HR, hormone receptors; HER2, Human Epidermal Growth Factor 2; IHC, immunohistochemistry; FISH, Fluorescence in situ hybridization; BCS, breast-conserving surgery; ET, endocrine therapy; CT, chemotherapy.

a Calculated on the HR+ population.

b Calculated on the HER2+ population.

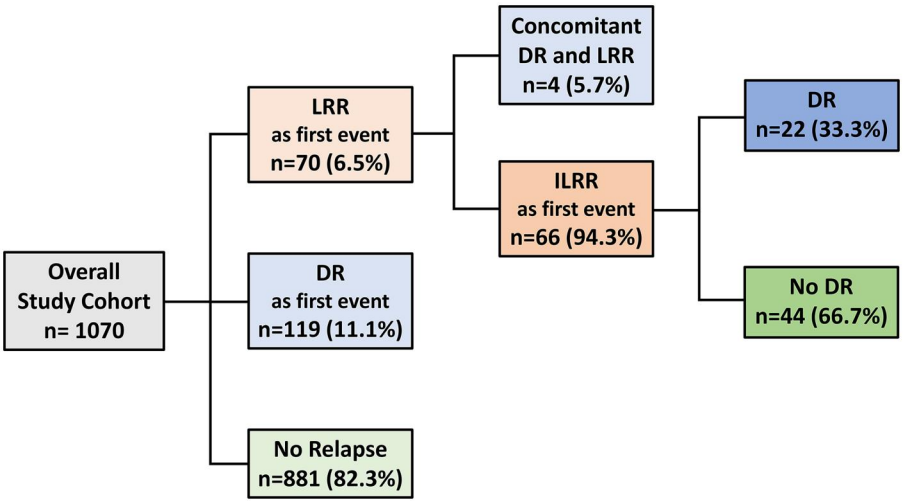

Figure 1. Diagram summarizing the type of relapse in the total population. LRR, locoregional recurrence, DR, distant recurrence, ILRR, isolated locoregional relapse.

Table 2. Patients' characteristics at the diagnosis of locoregional relapse as first event ($N = 66$).

		N (%)
Grade	1	0 (0)
	2	19 (29)
	3	16 (24)
	Missing	31 (47)
ER	Negative	12 (18)
	Positive	49 (74)
	Missing	5 (8)
PgR	Negative	20 (30)
	Positive	40 (61)
	Missing	6 (9)
HER2 (IHC/FISH)	Negative	49 (74)
	Positive	11 (17)
	Missing	6 (9)
HR loss[a]	No	46 (87)
	Yes	7 (13)
Breast Surgery type	BCS	27 (41)
	Mastectomy	33 (50)
	Missing	6 (9)
ET[a]	No	2 (4)
	Yes	47 (96)
CT	No	47 (71)
	Yes	14 (21)
	Missing	5 (8)
Trastuzumab[b]	No	5 (45)
	Yes	6 (55)
Distant relapse	No	44 (67)
	Yes	22 (33)

Abbreviations: *N*, number; ER, estrogen receptor; PgR, progesterone receptor; HR, hormone receptors; HER2, Human Epidermal Growth Factor 2; IHC, immunohistochemistry; FISH, Fluorescence in situ hybridization; BCS, breast-conserving surgery; ET, endocrine therapy; CT, chemotherapy.

a Calculated on the HR+ population.

b Calculated on the HER2+ population.

All the 66 patients who developed an ILRR as first event underwent surgical resection of the tumor relapse. Information on the type of surgical treatment was available for 60 patients (91%); of these, around half (55%, $N = 33$) underwent demolitive surgery (mastectomy).

Complete data regarding systemic treatment received after diagnosis of ILRR were available for 61 patients; among these, 14 (23% of available cases) received adjuvant chemotherapy and almost all patients diagnosed with an HR-positive ILRR (47/49, 96%) received adjuvant endocrine treatment. Only 6 (55%) of the 11 patients diagnosed with an HER2-positive ILRR received adjuvant trastuzumab.

Information regarding the specific localization of ILRR and the potential administration of adjuvant radiotherapy was not registered.

DRFI, DRFI from time of ILRR diagnosis and prognostic factors

In the overall study population ($N = 1070$), 145 patients (14%) experienced a distant recurrence. Overall median DRFI was 159 months (110-193 months).

As expected, significant differences in DRFI according to clinicopathological features at diagnosis (T and N status, type of surgery, and grade) were observed at univariate Cox regression model (Supplementary Table S2).

Patients diagnosed at a more advanced T and N stage, patients who underwent mastectomy for primary BC and patients diagnosed with poorly differentiated tumors all presented a significantly worse prognosis. On the other hand, HR and HER2 status did not show a significant impact on outcome. When assessing systemic treatments at primary BC diagnosis, administration of HT was significantly associated with better prognosis in patients with HR+ BC (HR for DRFI in HR+ subgroup 0.64, 95% CI 0.41-0.99, $P = .047$).

Among the 145 patients who presented a distant recurrence, 4 concomitantly presented an LRR, while 22 patients had previously presented an ILRR event (Figure 1).

Indeed, having presented an ILRR was significantly associated with a higher risk of developing a distant recurrence in the overall study population (Figure 2; log-rank $P < .001$).

In the subgroup of patients with ILRR ($N = 66$), 22 (33.3%) experienced a subsequent DR, with a median DRFI from ILRR diagnosis (DRFI post-ILRR) of 36 months (25-70 months).

Interestingly, a more advanced disease stage at first diagnosis was still associated with worse DRFI after ILRR. Indeed, extent of nodal involvement at first BC diagnosis was significantly associated with worse DRFI (patients with N3 tumors presented a significantly worse DRFI post-ILRR as compared with those with node-negative disease: HR 5.48, 95% CI 1.16-25.95; $P = .032$), and patients with larger tumors at first diagnosis showed a trend towards worse DRFI post-ILRR, although not statistically significant (pT4 versus pT1: HR 7.62, 95% CI 0.94-62.02; $P = .058$) (Table 3). On the contrary, histological grade, HR and HER2 status evaluated on the primary BC were not associated with significant differences in DRFI post-ILRR (Table 3).

However, HER2-positivity assessed on the ILRR was significantly associated with a worse DRFI post-ILRR (HR 3.43, 95% CI 1.27-9.26; $P = .015$), while histological grade and HR status evaluated on the relapse were not significantly associated with DRFI post-ILRR. Consistently, we did not observe a significant association between HR loss on the relapse (conversion from HR positive on the primary tumor to HR negative on the ILRR) and DRFI post-ILR (log-rank $P = .178$; Supplementary Figure S1a).

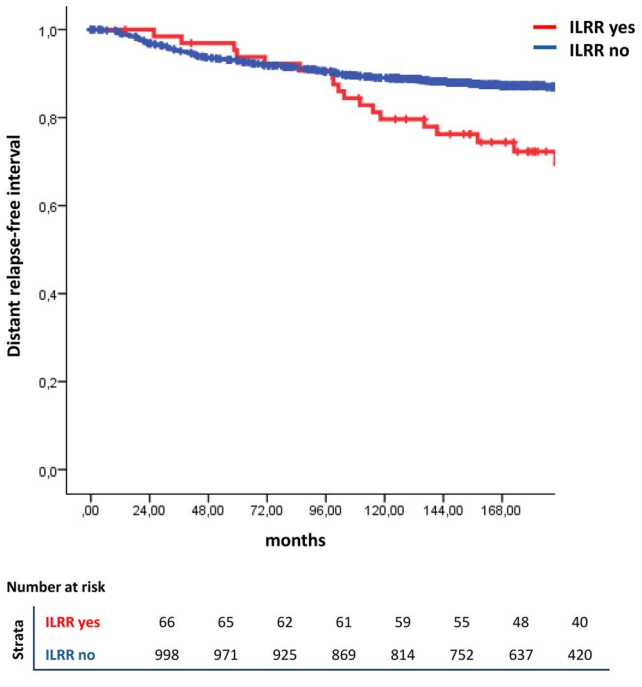

Figure 2. Distant relapse-free interval according to the presence of a previous ILRR in the overall population. ILRR, isolated locoregional relapse.

When considering treatment administered at the time of ILRR, patients who received chemotherapy showed a non-statistically significant trend towards a better DRFI post-ILRR (HR 0.17, 95% CI 0.02-1.26; $P = .082$). The magnitude of this effect appeared less evident for patients with HR+ ILRR (HR 0.35 95% CI 0.05-2.64; $P = .309$) as compared with patients with HR− ILRR (0.11 95%CI 0.00-142; $P = .352$). However, the power of this analysis was significantly limited by the small patient population. The effect of administration of HT in patients with HR+ ILRR could not be assessed in our study cohort as almost all these patients received this treatment.

In multivariable analysis, nodal involvement at primary diagnosis remained independently associated with DRFI post-ILRR (pN3 vs pN0: HR 10.04, 95% CI 1.69-59.74; $P = .011$), while HER2 positivity at recurrence showed a consistent trend towards worse outcomes (HR 2.68, 95% CI 0.91-7.98; $P = .075$) (Table 3).

In an exploratory multivariable analysis adjusting for nodal status at primary diagnosis and HER2 status at ILRR, the administration of chemotherapy for the recurrence was associated with improved DRFI post-ILRR (HR 0.12, 95% CI 0.02-0.93; $P = .043$) (Supplementary Table S3), although these findings should be interpreted with caution due to the limited sample size.

OS, OS from time of ILRR diagnosis and prognostic factors

In the overall study population ($N = 1070$), an overall survival (OS) rate of 72% was observed at 15 years from the first BC diagnosis.

As expected, patients who experienced a DR presented a significantly worse OS as compared with those without DR (log-rank $P < .001$, Figure 3A). However, no significant association between ILRR and a worse OS was observed (log-rank $P = .248$, Figure 3B).

Given that ILRR occurs during follow-up and cannot be considered a baseline characteristic, additional analyses were performed to account for potential immortal time bias. In a time-dependent Cox model, in which ILRR was included as a time-varying covariate, the ILRR was significantly associated with shorter OS (HR 2.16, 95% CI 1.44-3.24, $P < 0.001$). A sensitivity landmark analysis, including only patients alive and under follow-up at 3 and 5 years from primary diagnosis, also confirmed the worse outcome in patients who develop an ILRR (Supplementary Figure S2a and S2b).

In the subgroup of patients who presented an ILRR ($N = 66$), median OS from ILRR (OS post-ILRR) was 75 months (48-121 months).

Similarly to what was observed for DRFI post-ILRR, among clinico-pathological features at first BC diagnosis, only extent of nodal involvement at first BC diagnosis was significantly associated with OS post-ILRR (patients with N3 tumors presented a significantly worse OS post-ILRR as compared with those with node negative disease: HR 5.06 95% CI 1.03-24.83, $P = .046$), while patients with larger tumors at first diagnosis showed a trend towards worse OS post-ILRR, although not statistically significant (HR 6.77 95% CI 0.85-54.07, $P = .071$ for T4 as compared with T1) (Table 4).

Patients who were pre-menopausal at first diagnosis showed a not-statistically significant trend towards better OS post-ILRR

Table 3. Uni- and multivariate Cox regression model for DRFI-post ILRR according to clinico-pathological features and treatment for primary BC and for ILRR.

			Univariate analysis		Multivariate analysis	
			HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
	Primary tumor					
Menopause	Post	26 (39)	Ref			
	Pre	40 (61)	0.79 (0.34-1.85)	.584		
pT	1	47 (73)	Ref			
	2	14 (22)	1.35 (0.51-3.56)	.551		
	3	2 (3)	1.44 (0.18-11.24)	.729		
	4	1 (2)	7.62 (0.94-62.02)	.058		
pN[a]	0	39 (61)	Ref		Ref	
	1	22 (34)	0.86 (0.34-2.16)	.749	0.99 (0.36-2.68)	.981
	3	**3 (5)**	**5.48 (1.16-25.95)**	**.032**	**10.04 (1.69-59.74)**	**.011**
Grade	1/2	43 (70)	Ref			
	3	18 (30)	1.16 (0.47-2.85)	.746		
HR	Pos	58 (88)	Ref			
	Neg	8 (12)	4.39 (0.59-32.40)	.150		
HER2	Neg	38 (81)	Ref			
(IHC/FISH)	Pos	9 (19)	1.76 (0.47-6.56)	.402		
Breast Surgery	BCS	49 (75)	Ref			
Type	Mastectomy	16 (25)	2.06 (0.87-4.88)	.103		
ET[b]	No	16 (25)	Ref			
	Yes	49 (75)	0.96 (0.37-2.46)	.093		
CT	No	28 (42)	Ref			
	Yes	38 (58)	0.66 (0.28-1.55)	.340		
	ILRR					
Grade	2	19 (54)	Ref			
	3	16 (46)	1.08 (0.31-3.77)	.908		
HR loss[c]	No	46 (87)	Ref			
	Yes	7 (13)	2.26 (0.64-8.07)	.208		
HR	Pos	49 (80)	Ref			
	Neg	12(20)	1.52 (0.44-5.20)	.508		
HER2	Neg	49 (82)	Ref		Ref	
(IHC/FISH)	Pos	**11 (18)**	**3.43 (1.27-9.26)**	**.015**	2.68 (0.91-7.98)	.075
CT	No	47 (77)	Ref			
(all)	Yes	14 (23)	0.17 (0.02-1.26)	.082		
CT	No	41 (84)	Ref			
(HR+)	Yes	8 (16)	0.35 (0.05-2.64)	.309		
CT	No	6 (50)	Ref			
(HR−)	Yes	6 (50)	0.11 (0.00-142)	.352		

Abbreviations: HR, hazard ratio; Ref, reference; HR, hormone receptors; HER2, Human Epidermal Growth Factor 2; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; BCS, breast-conserving surgery; ET, endocrine therapy; CT, chemotherapy; ILRR, isolated locoregional relapse.

a In this patient cohort, no patient presented a pN2 at initial diagnosis.

b From HR+ primary tumor to HR− relapsing tumor.

c Evaluated on patients with HR+ primary tumor.

(HR 0.44, 95% CI 0.19-1.02, *P* = .056), as compared with patients who were already post-menopausal (potentially a proxy for older age at BC diagnosis). In addition, patients who received chemotherapy at first diagnosis presented a better OS post-ILRR (HR 0.43 95% CI 0.20-0.93, *P* = .032). Histological grade, HR and HER2 status evaluated on the primary BC were not associated with significant differences in OS post-ILRR (Table 4). On the contrary, HER2-positivity assessed on the ILRR was significantly associated with a worse OS post-ILRR (HR 3.40, 95% CI 1.34-8.60 *P* = .010). HR status and G evaluated on the ILRR were not associated with significant differences in OS. However, among patients initially diagnosed with HR+ BC, switching to an HR-negative status on the ILRR was significantly associated with a worse OS post-ILRR (HR 3.26 95% CI 1.07-9.90, *P* = .037; Supplementary Figure S1b).

When considering treatment administered at the time of ILRR, patients who received chemotherapy showed a trend towards a better OS post-ILRR(HR 0.31 95% CI 0.07-1.31, *P* = .111). Again,

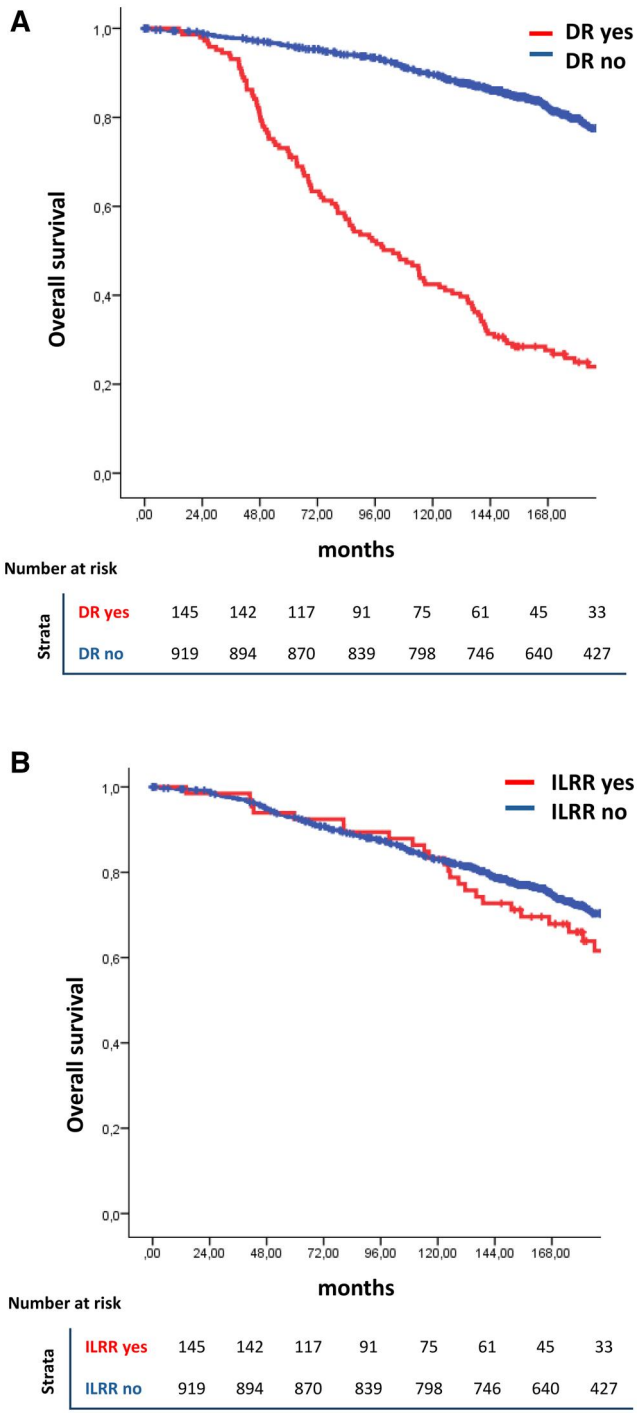

Figure 3. Kaplan–Meier curve for overall survival (OS) for patients with previous diagnosis of a distant recurrence (DR) versus not (A) and for patients with previous diagnosis of ILRR versus not (B). ILRR, isolated locoregional relapse.

the magnitude of this effect appeared less evident for patients with HR+ ILRR (HR 0.34 95% CI 0.05-2.59, $P = .300$) as compared with patients with HR– ILRR (HR 0.19 95% CI 0.02-1.71, $P = .139$), although the power of this analysis was significantly limited by the small patient population.

In multivariable analysis, nodal involvement at primary diagnosis and HER2 positivity assessed on the recurrence remained independently associated with OS post-ILRR (HR 5.97, 95% CI 1.11-32.00, $P = .037$ for respectively pN3 vs pN0 primary tumor and HR 3.15, 95% CI 1.15-8.64, $P = .026$ for HER2+ ILRR compared with HER2-) (Table 4).

In an exploratory multivariable analysis adjusting for nodal status at primary diagnosis and HER2 status at recurrence, the administration of chemotherapy at the time of ILRR showed a non-statistically significant trend towards improved OS post-ILRR (HR 0.23, 95% CI 0.05-1.11; $P = .067$) (Supplementary Table S4). Nevertheless, this finding should be interpreted with caution given the limited sample size.

Discussion

Locoregional relapse after radical treatment for BC represents a challenge in terms of diagnosis and management and it is a recognized risk factor for distant failure.

We present data on long-term outcomes of a large retrospective mono-institutional database of patients treated for primary BC between 2000 and 2007.

We reported an ILRR rate of 6%, in line with previously published data.[9–13] However, we did not observe a significant association between main clinico-pathological factors and risk of developing ILRR, an observation in contrast with other studies that reported a significant modulation of risk of ILRR according to HR status, grade, and patient age.[14,15] Nevertheless, this result might also be linked to the relatively small number of ILRR events analyzed in the present study. Intriguingly, we observed a trend towards a protective role of chemotherapy administration for locoregional failure, possibly related to a higher relative benefit in patients who are considered at higher risk of relapse. On the other hand, endocrine treatment in patients with HR+ BC was only prognostic for distant relapse, but not for ILRR.

As expected, a worse DRFI was observed in patients with a more advanced stage at diagnosis, confirming the unquestionable role of traditional clinico-pathological factors (such as tumor dimension and nodal status) in determining BC prognosis. In addition, a previous diagnosis of ILRR also represented a significant negative prognostic factor for DRFI, consistently with previous evidence.[5] Indeed, in our study cohort, one third of patients with an ILRR were subsequently diagnosed with distant recurrence in the following years. This very high risk highlights the crucial relevance and the open challenges that the treatment of ILRR still poses. In the overall cohort, we initially did not observe a significant association between ILRR and OS when ILRR was treated as a time-fixed variable. However, in a time-dependent Cox model, ILRR emerged as a negative prognostic factor for OS. This finding was further confirmed in both 3-year and 5-year landmark analyses.

Importantly, in multivariate analyses, nodal involvement at primary diagnosis remained independently associated with both DRFI and OS after ILRR, further supporting the prognostic role of initial tumor burden even in the setting of recurrent disease.

We also examined the role of clinico-pathological features of primary tumor on outcome after ILRR, both in terms of DRFI post-ILRR and OS post-ILRR. Indeed, a larger primary tumor dimension and greater nodal involvement at first BC diagnosis were significantly associated with a worse outcome after ILRR

Table 4. Uni- and multivariate Cox regression model for OS-post ILRR according to clinico-pathological features and treatment for primary BC and for ILRR.

		Univariate analysis			Multivariate analysis	
		N (%)	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
	Primary tumor					
Menopause	Post	40 (61)	Ref			
	Pre	26 (39	0.44 (0.19-1.02)	.056		
pT	1	47 (73)	Ref			
	2	14 (22)	1.74 (0.72-4.25)	.222		
	3	2 (3)	3.03 (0.67-13.76)	.152		
	4	1 (2)	6.77 (0.85-54.07)	.071		
pN[a]	0	39 (61)	Ref		Ref	
	1	22 (34)	0.38 (0.14-1.02)	.054	0.49 (0.14-1.76)	.276
	3	**3 (5)**	**5.06 (1.03-24.83)**	**.046**	**5.97 (1.11-32.00)**	**.037**
Grade	1/2	43 (70)	Ref			
	3	18 (30)	1.18 (0.51-2.73)	.693		
HR	Pos	58 (88)	Ref			
(primary)	Neg	8 (12)	2.72 (0.63-11.69)	.178		
HER2	Neg	38 (81)	Ref			
(IHC/FISH)	Pos	9 (19)	1.31 (0.36-4.70)	.680		
Breast	BCS	49 (76)	Ref			
Surgery Type	Mastectomy	16 (24)	1.01 (0.43-2.38)	.974		
ET[b]	No	9 (16)	Ref			
	Yes	48 (84)	0.68 (0.25-1.81)	.435		
CT	No	28 (42)	Ref		Ref	
	Yes	**38 (58)**	**0.43 (0.20-0.93)**	**.032**	0.70 (0.26-1.88)	.475
	ILRR					
Grade	2	19 (54)	Ref			
	3	16 (46)	0.76 (0.22-2.61)	.665		
HR loss[c]	No	41 (85)	Ref		Ref	
	Yes	7 (15)	3.35 (1.07-10.42)	**.037**	2.72 (0.15-2.24)	.149
HR	Pos	49 (80)	Ref			
	Neg	12 (20)	1.05 (0.39-2.84)	.929		
HER2	Neg	49 (82)	Ref		Ref	
(IHC/FISH)	Pos	**11 (18)**	**3.40 (1.34-8.60)**	**.010**	**3.15 (1.15-8.64)**	**.026**
CT	No	47 (77)	Ref			
(all)	Yes	14 (23)	0.31 (0.07-1.31)	.111		
CT	No	41 (84)	Ref			
(HR+)	Yes	8 (17)	0.34 (0.05-2.59)	.300		
CT	No	6 (50)	Ref			
(HR−)	Yes	6 (50)	0.19 (0.21-1.71)	.139		
Trastuzumab	No	5 (45)	Ref			
(HER2+)	Yes	6 (55)	1.37 (0.30-6.17)	.683		

Abbreviations: HR, hazard ratio; Ref, reference; HR, hormone receptors; HER2, Human Epidermal Growth Factor 2; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; BCS, breast-conserving surgery; ET, endocrine therapy; CT, chemotherapy; ILRR, isolated locoregional relapse.

a In this patient cohort, no patient presented a pN2 at initial diagnosis.

b Evaluated on patients with HR+ primary tumor.

c From HR+ primary tumor to HR− relapsing tumor.

development. In addition, biological features of ILRR were also observed to significantly impact patient prognosis after ILRR. Patients who developed an HER2-positive ILRR presented a worse DRFI and OS post-ILRR, and the loss of HR-positivity on the ILRR was significantly associated with a worse OS after ILRR, as previously reported in some studies.[16] Based on these evidence, histopathological examination and biological recharacterization of the relapse are crucial to obtain prognostic information and to potentially guide treatment choice.

To date, advances in surgical and radiotherapy techniques allow the consideration of repeated lumpectomy and re-irradiation, when feasible, for the local treatment of LRR. In our population, a second breast conservative surgery after ILRR was performed in almost half of the cases. For what concerns the

use of adjuvant systemic therapy for BC patients presenting an ILRR, data from only two randomized trials are available, evaluating the role of adjuvant endocrine treatment and of adjuvant chemotherapy, respectively.[6,7] Taken together, evidence from the CALOR and the SAKK 23/82 trial confirms the efficacy of endocrine therapy in patients with HR+ disease and supports the use of adjuvant chemotherapy in patients with HR− disease. Indeed, in a multivariate analysis of the CALOR study, HR status on the locoregional relapse appeared to be a predictor of chemotherapy benefit. In our study cohort, when considering systemic treatment administered at time of ILRR, we only observed a numerically better DRFI post-ILRR for patients who received chemotherapy. However, the limited number of events potentially limited the statistical power of this analysis. In an exploratory multivariate analysis adjusting for key prognostic factors, the administration of chemotherapy was associated with improved DRFI after ILRR, suggesting a potential benefit in selected patients. Nevertheless, a potentially less pronounced effect of cytotoxic treatment on DRFI post-ILRR was observed for HR+ ILRR as compared with HR− ILRR, a result consistent with data from the CALOR study. On the other side, we could not dissect the impact of HT in patients with HR+ disease in our study cohort, as almost all these patients received HT.

Our study presents some limitations. First, due to the retrospective nature, we could not fully describe the pattern of ILRR from clinical records. Moreover, we lacked information on radiotherapy for both primary and recurrent disease, which could potentially have affected the type of local treatment performed at relapse and the risk of recurrence. In fact, the choice of repeating a conservative surgery of recurrent tumors is deeply dependent from the technical feasibility of a second radiotherapy and should be discussed in multidisciplinary team. Furthermore, having received a breast conserving surgery without following adjuvant radiotherapy should be considered as an undertreatment, with obvious impact of the risk of relapse. In addition, due to the years considered in this study, evaluation of HER2 status was limited to a subgroup of patients, and only a part of patients with HER2+ disease received anti-HER2 therapy at first diagnosis or after local relapse. This bias could impact, on one hand, the role of HER2 positivity on the risk of a subsequent BC-related event, and, on the other hand, mitigates our observation of a worse outcome in case of HER2+ ILRR. Moreover, despite the inclusion of parsimonious multivariable models, the relatively small number of events after the ILRR represents an important limitation, potentially affecting both the stability of the estimates and our ability to reliably assess the impact of specific treatments on post-ILRR outcome.

Moreover, as is often the case in retrospective studies assessing breast cancer patients, distinguishing between a true relapse and a new primary tumor represented a significant challenge, with a potential risk of overestimation of the ILRR events. Still, as we specified in the Methods of the study, according to the STEEP criteria, we considered an ipsilateral invasive tumor after primary surgery as a locoregional relapse.[17]

To our knowledge, this is one of the biggest datasets of consecutive real-world BC patients treated at a single institution, with a very long follow up. Our findings confirm that clinical-pathological features at first BC diagnosis, such as greater tumor dimension and grade of nodal involvement, are associated with worse prognosis after an ILRR and that patients who present an ILRR have a considerably higher risk of developing distant metastases. For what concerns systemic treatment after ILRR, the benefit of chemotherapy has been reported to be mainly observed in HR− disease and data regarding the potential use of CDK4/6 inhibitors, in addition to the already widely used HT, in HR+ ILRR are awaited. In this context, our observation that switching from a HR-positive primary tumor to a HR-negative ILRR is associated with a significantly worse post-ILRR OS highlights the fundamental role of biological characterization of the relapse to better predict patients' prognosis. Besides, considering that HR status remains a predictive factor for systemic therapy, its evaluation in a relapsing tumor is imperative to tailor treatment choice.

Conclusion

The treatment decision process for the treatment of an ILRR after BC diagnosis poses significant challenges, especially for the need to consider the heterogeneity of previous therapies. Given the not negligible rate of ILRR, and its negative prognostic impact, a prompt diagnosis and treatment are crucial. In this complex scenario, real-world studies offer a unique opportunity to identify potential factors stratifying patients' prognosis allowing personalization of treatment and follow-up after ILRR.

Author contributions

Grazia Vernaci (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Gaia Griguolo (Formal analysis, Investigation, Methodology, Writing—review & editing), Fabio Girardi (Investigation, Methodology, Writing—review & editing), Alice Menichetti (Investigation, Writing—review & editing), Massimo Ferrucci (Investigation, Writing—review & editing), Alberto Marchet (Investigation, Writing—review & editing), Luisa Bellu (Investigation, Writing—review & editing), Giovanni Faggioni (Investigation, Writing—review & editing), Cristina Falci (Investigation, Writing—review & editing), Giusy Landa (Investigation, Writing—review & editing), Marina La Commare (Investigation, Writing—review & editing), Tommaso Giarratano (Investigation, Writing—review & editing), Carlo Alberto Giorgi (Investigation, Writing—review & editing), Valentina Guarneri (Conceptualization, Investigation, Methodology, Writing—review & editing), and Maria Vittoria Dieci (Conceptualization, Investigation, Methodology, Writing—review & editing)

Supplementary material

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Conflicts of interest

G.V. reports personal fees from Novartis, Daiichi Sankyo and Astrazeneca; travel expenses from Roche. G.G. reports fees for advisory role from Gilead, Seagen, Menarini; personal fees as an invited speaker from EliLilly, Novartis, MSD. F.G. reports Honoraria for lecture from Eli Lilly, Gilead; Consulting fees from World Health Organization; Support for attending meetings and travel from Eli Lilly, Gilead, Novartis. T.G. reports Congress Honoraria and fees from Novartis, Eli Lilly, Daiichi Sankyo, Astrazeneca, Seagen. C.A.G. reports personal fees from Novartis, Ely Lilly, Astrazeneca, Daiichi Sankyo, MSD, Seagen. V.G. reports personal fees for advisory board participation for AstraZeneca, Daiichi-Sankyo, Eli Lilly, Gilead, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Menarini Stemline, Exact Sciences; personal fees as an invited speaker for AstraZeneca, Daiichi-Sankyo, Eli Lilly, Exact Sciences, Gilead, GSK, Novartis, Roche, Zentiva, Menarini Stemline; personal fees for expert testimony for Eli Lilly, patents for HER2DX (Institution). M.V.D. reports personal fees for consultancy/advisory role from Eli Lilly, Pfizer, Novartis, Seagen, Gilead, MSD, Exact Sciences, AstraZeneca, Roche, Daiichi-Sankyo, Roche. The other authors have nothing to disclose.

Data availability

Data are property of the corresponding author and available upon request.

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