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BRIEF COMMUNICATION

Pattern and risk factors of isolated local relapse among women with hormone receptor-positive and HER2-negative breast cancer and lymph node involvement: 10-year follow-up analysis of the PACS 01 and PACS 04 trials

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Abstract

Purpose We aimed to determine the pattern of isolated local recurrences (ILR) in women with stage II-III hormone receptor-positive and human epidermal growth factor receptor 2 breast cancer (HR + /HER2-BC) after 10-year follow-up.

Methods UNICANCER-PACS 01 and PACS 04 trials included 5,008 women with T1-T3 and N1-N3 to evaluate the efficacy of different anthracycline ± taxanes-containing regimens after modified mastectomy or lumpectomy plus axillary lymph node dissection. We analyzed the data from 2,932 women with HR + /HER2- BC to evaluate the cumulative incidence of ILR and describe the factors associated with ILR.

Results After a median follow-up of 9.1 years (95% CI 9.0–9.2 years), the cumulative incidence of ILR increased steadily between 1 and 10 years from 0.2% to 2.5%. The multivariable analysis showed that older age (subhazard ratios [sHR] = 0.95, 95% CI 0.92–0.99) and mastectomy (sHR = 0.39, 95% CI 0.17–0.86) were associated with lower risk of ILR, and no adjuvant endocrine therapy (sHR = 2.73, 95% CI 1.32 7–5.67) with increased risk of ILR.

Conclusion In this population of high-risk patients with localized HR + /HER2- BC, the risk of ILR was low but remained constant over 10 years. Younger age at diagnosis, breast-conserving surgery, and adjuvant endocrine therapy were independent risk factors of ILR.

Keywords Breast cancer · Lymph node · Local recurrence · Local relapse · Recurrence

Introduction

More than 90% of women with breast cancer present a local or locoregional disease (stage I-III) at diagnosis and can be treated in a curative intent through a multidisciplinary approach that optimally combines local and systemic therapies [1, 2]. A proportion of these patients remains at risk of developing distant, regional, or local recurrences. For women treated for early breast cancer, the risk of recurrences in the ipsilateral breast, chest wall, or regional lymph nodes at 10 year ranges between 4% and 7–17% following mastectomy or breast-conserving therapy plus radiotherapy, respectively [3–6]. Published data have shown that the likelihood of locoregional relapse may be impacted by the omission of adjuvant radiotherapy, presence of positive surgical margins, younger patient age (< 40 years) at diagnosis, larger tumor size, higher tumor grade, presence of lymphovascular invasion, and absence of hormone receptors in the tumor [7–11]. Notably, hormone receptor-positive (HR +) and human epidermal growth factor receptor 2-negative (HER2-) breast cancers (HR + /HER2- BC) exhibit the lowest risk of locoregional relapse compared to HER2-positive and triple-negative tumors after mastectomy and breast-conserving surgery [9].

The advances in therapeutic approaches over the last two decades have modified the recurrence patterns of

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early and locally advanced breast cancers and substantially reduced the incidence of distant and locoregional recurrences [12–16]. However, little is known about the risk and pattern of late isolated local recurrences (ILR) in patients with HR + /HER2- BC treated with modern local and systemic approaches. This study aims to analyze the cumulative incidence and the time-specific risk of ILR over a 10-year follow-up and the associated risk factors, in two large randomized studies of patients with stage II-III HR + / HER2- BC.

Materials and methods

Studies overview

This retrospective analysis used prospectively collected individual-participant data from 6,523 women from the two randomized clinical trials FNCLCC-PACS 01 and PACS 04 which aimed at evaluating the efficacy of different anthracycline ± taxanes-containing regimens after modified mastectomy or lumpectomy plus axillary lymph node dissection in patients with T1-T3 and N1-N3 breast cancer [17, 18]. PACS 01 enrolled 1,999 patients between June 1997 and March 2000, and PACS 04 enrolled 3,009 patients between February 2001 and August 2004. The PACS 01 and 04 trials required a written informed consent signed by each patient before randomization. The studies were coordinated by the National French Cancer Centers Cooperative Group (UNICANCER), reviewed and approved by the ethics committee/institutional review board, and conducted according to the Declaration of Helsinki and European Good Clinical Practice requirements.

The study population for this analysis included 2,909 women with HR + /HER2- BC. Patients with a follow-up duration of less than one year and those who did not complete one cycle of adjuvant chemotherapy were excluded (Fig. 1). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Treatment and follow-up within the PACS 01 trial

The chemotherapy regimens evaluated in PACS 01 were fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, plus cyclophosphamide 500 mg/m^2 (FEC) intravenously on day 1 every 21 days for six cycles ($n = 408$), and FEC for 3 cycles followed by docetaxel (D) 100 mg/m^2 intravenously on day 1 every 21 days for 3 cycles ($n = 428$). Radiotherapy was initiated within 4 weeks after the last cycle of chemotherapy and was mandatory for all patients who had undergone breast-conserving surgery. Radiation to the chest wall, supraclavicular area, and internal mammary chain was recommended

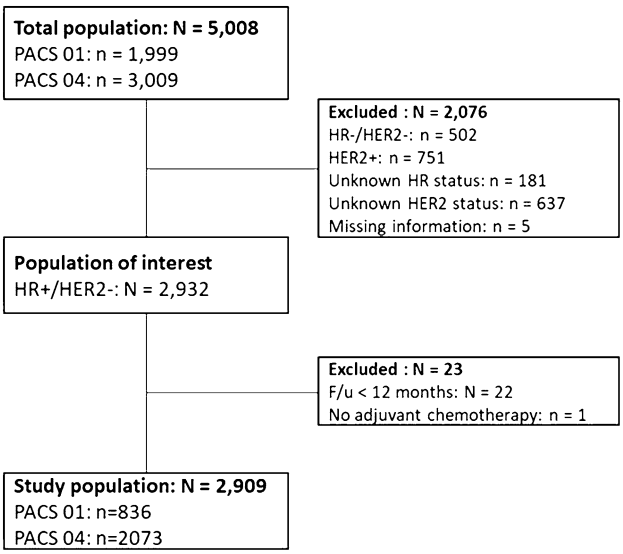

Fig. 1 Flowchart of the study population

following mastectomy. Irradiation of the axilla was prohibited. Tamoxifen 20 mg/d was started after chemotherapy completion and continued for 5 years.

During follow-up, a physical examination was performed every 4 months for the first 2 years then every 6 months for the years 3 to 5 and annually thereafter. Imaging studies (mammography, chest x-ray, liver ultrasound, and bone scan) were performed 1 year after the initial surgery, then yearly until year 5.

Treatment and follow-up within the PACS 04 trial

The chemotherapy regimens evaluated in PACS 04 were fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, plus cyclophosphamide 500 mg/m^2 (FEC) intravenously on day 1 every 21 days for six cycles ($n = 1,031$) and epirubicin 75 mg/m^2 plus docetaxel 75 mg/m^2 (ED75) intravenously on day 1 every 21 days for 6 cycles ($n = 1,042$). Radiotherapy began within 4 weeks after chemotherapy completion. Regional lymph node irradiation was mandatory for all patients and breast irradiation in case of breast-conserving surgery. Premenopausal women were prescribed tamoxifen 20 mg per day for five years and postmenopausal women were prescribed a non-steroidal aromatase inhibitor (anastrozole/letrozole) or tamoxifen for five years. The choice of endocrine therapy (non-steroidal aromatase inhibitor or tamoxifen) was left at the discretion of investigator for postmenopausal women.

During follow-up, a physical examination was performed every 4 months for the first 2 years, every 6 months for the following 3 years, and annually thereafter. Annual examination included complete blood tests, mammography, liver ultrasound, bone scan, and chest X-ray until year 5.

Outcomes and study covariates

Our main objective was to evaluate the cumulative incidence of ILR in patients with stage II-III HR + /HER2- BC. An isolated local relapse was defined by the occurrence of any invasive carcinoma or ductal carcinoma in situ in the skin or parenchyma of the ipsilateral breast, without any clinical or radiological evidence of distant disease [19]. The competing event was defined by the occurrence of any breast cancer recurrence other than ILR; it included nodal recurrences, distant recurrences, contralateral primary breast cancer, any second malignancy, and death from any cause without ILR. Time to ILR or competing event was calculated from study randomization to diagnosis of ILR or competing event based on which recurrence came first. Because the timing of testing could influence the determination of the first event, we consider as ILR only patients who did not present any other event within three months from the first diagnosis of ILR. For example, simultaneous (within 3 months) ILR and distant metastasis would have first event classified as distant metastasis. In the overall population, disease-free survival (DFS) and overall survival (OS) were defined by the delay between randomization and event of interest using the following first-event definitions: death for overall survival, any breast cancer recurrence (including ILR, nodal recurrences, distant recurrences or controlateral primary breast cancer), any second malignancy, and death from any cause for disease-free survival.

Statistical analysis

Descriptive statistics were used to summarize patient, tumor, and treatment characteristics at study randomization. Survival rates and follow-up were estimated using the Kaplan–Meier and reverse Kaplan–Meier methods, respectively. In a compering risks analysis, the cumulative incidence associated with each event was estimated by a Kalbfleisch–Prentice estimator. Uni- and multivariable analyses were conducted using Fine and Gray model to identify the factors associated with ILR appearance. Subhazard ratios (sHRs) were estimated with 95% confidence interval (95% CI). A sHR greater than one implies a constant relative increase and a higher cumulative incidence. All p values were two-sided and considered statistically significant below 0.05. All statistical analyses were performed using STATA 12 software.

Results

A total of 2,909 women from the PACS 01 and 04 trials were included in this analysis (Fig. 1). The median age at diagnosis was 50 years (range 22–65 years) with 3.9% of women younger than 35 years of age. Median tumor size was 2 cm (range 0.2–18 cm). Table 1 summarizes patient, tumor, and treatment characteristics at baseline. The treatment strategy predominately involved breast-conserving surgery ($n = 1,954$; 67.2%) followed by an adjuvant chemotherapy (median 6 [range 1–6] cycles), radiotherapy ($n = 2,826$; 97.3%), and endocrine therapy ($n = 2,667$; 92.2%).

After a median follow-up of 9.1 years (95% CI 9.0–9.2 years), the 10-year DFS and OS were 68.6% and 82.7%, respectively. Local recurrences occurred in 90 patients (3.1%). The competing events included distant metastases ($n = 537$, 18.5%), contralateral breast cancer ($n = 106$, 3.6%), second malignancy ($n = 86$; 3.0%), and nodal recurrence ($n = 66$, 2.3%). The cumulative incidence of ILR increased steadily between 1 and 10 years from 0.2% to 2.5% and that of the competing events increased sharply from 1.3% to 29.1% (Fig. 2). Among the 60 women who experienced ILR (without competing events), the median time from study randomization to ILR was 59.7 months (range 1.2–133.9 months). The multivariable analysis showed that older age (sHR = 0.95, 95% CI 0.92–0.99) and mastectomy (sHR = 0.39, 95% CI 0.17–0.86) were associated with lower risk of ILR, and no adjuvant endocrine therapy (sHR = 2.73, 95% CI 1.32 7–5.67) was associated with increased risk of ILR (Tables 2 and 3).

Discussion

In this study, we aimed to assess the patterns of recurrence among women with HR + /HER2- BC and lymph node involvement that were included in the PACS 01 and 04 trials. We specifically focused on the occurrence of ILR because patients with ILR have a higher likelihood of distant relapses and increased cancer-specific death, particularly when ILR occurs early in the post-treatment trajectories [20–22]. Published data of breast cancer patients with and without hormone receptor expression showed that patients with ILR remain at higher risk of distant failure and breast cancer-specific death at 20 years from the first diagnosis [22]. Patients with HR + /HER2- BC had the lowest rates of local recurrence with a 5-year local relapse rate of 0.8–2.9% for HR + tumors after breast-conserving surgery and adjuvant therapy [23–26]. Furthermore, the advances in surgical and radiation techniques along with a wider and extended use of adjuvant systemic therapies have reduced the rate of local recurrences in patients with luminal breast cancers [24, 27–30]. Our findings are consistent with previous findings as 60 patients (2.1%) experienced ILR as the first event after a median follow-up of 9.1 years. Interestingly, we found that the cumulative incidence of ILR increased steadily over time from 0.2% at 1 year to 1.0% at 5 years and reached 2.5% at 10 years. The pattern of recurrences differed between ILR

Table 1 Patient, tumor, and treatment characteristics at baseline

Patient and tumor characteristics		Overall ($N=2,909$)	PACS 01 ($N=836$)	PACS 04 ($N=2,073$)
Age	< 40 years	324 (11.1%)	98 (11.7%)	226 (10.9%)
	40–50 years	2265 (77.9%)	643 (76.9%)	1622 (78.2%)
	> 60 years	320 (11.0%)	95 (11.4%)	225 (10.9%)
Body mass index	< 18.5 kg/m^2	97 (3.3%)	24 (2.9%)	73(3.5%)
	18.5–24.9 kg/m^2	1603 (55.1%)	476 (57.0%)	1127 (54.4%)
	≥ 25.0 kg/m^2	1207(41.6%)	335 (40.1%)	872 (42.1%)
	Missing	2	1	1
Histological tumor size	≤ 2 cm	1531 (54.4%)	416 (54.4%)	1115 (54.4%)
	2.1–5 cm	1109 (39.4%)	312 (40.8%)	797 (38.9%)
	> 5 cm	174 (6.2%)	37 (4.8%)	137 (6.7%)
Lymph node involvement	1–3	1967 (67.6%)	520 (62.2%)	1447 (69.8%)
	> 3	942 (32.4%)	316 (37.8%)	626 (30.2%)
Histological grade	Grade I	475 (16.6%)	116 (14.0%)	359 (17.7%)
	Grade II	1539 (53.9%)	414 (49.8%)	1125 (55.6%)
	Grade III	801 (28.1%)	262 (31.5%)	539 (26.6%)
	Not gradable	39 (1.4%)	39 (4.7%)	0 (0%)
Lymphovascular invasion	Yes	1071 (45.7%)	313 (54.3%)	758 (42.9%)
	No	1271 (54.3%)	263 (45.7%)	1008 (57.1%)
Histology	Ductal	2278 (78.6%)	616 (73.7%)	1662 (80.5%)
	Lobular	449 (15.5%)	133 (15.9%)	316 (15.3%)
	Other	173 (6.0%)	87 (10.4%)	86 (4.2%)
Hormone receptors expression	ER-/PR +	140 (5.1%)	52 (6.3%)	88 (4.5%)
	ER + /PR-	457 (16.5%)	146 (17.7%)	311 (16.0%)
	ER + /PR +	2168 (78.4%)	629 (76.1%)	1539 (79.4%)
	Missing	144	9	135
Surgery	BCS	1954 (67.2%)	508 (60.8%)	1446 (69.8%)
	Mastectomy	955 (32.8%)	328 (39.2%)	627 (30.2%)
Adjuvant chemotherapy	FEC × 6 cycles	1439 (49.5%)	408 (48.8%)	1031 (49.7%)
	ED × 6 cycles	1042 (35.8%)	0 (0%)	1042 (50.3%)
	FEC × 3 cycles + D × 3 cycles	428 (14.7%)	428 (51.2%)	0 (0%)
Radiotherapy	Yes	2826 (97.3%)	818 (98.3%)	2008 (96.9%)
	No	79 (2.7%)	14 (1.7%)	65 (3.1%)
	Missing	4	4	0
Endocrine therapy		2667 (92.2%)	635 (76.3%)	2032 (98.6%)
	Tamoxifen	2414 (90.5%)	635 (100%)	1779 (87.5%)
	Anastrazole/Letrozole	253 (9.5%)	0 (0%)	253 (12.5%)

BCS breast-conserving surgery, *C* cyclophosphamide, *D* docetaxel, *ER* estrogen receptor, *F* 5-fluorouracil, *PR* progesterone receptor

and distant metastases as the incidence of ILR remains quite constant over time and that of the competing events, mainly distant relapses, sharply increased from year 5 onward.

Several clinicopathological features and treatment characteristics have been consistently associated with a higher lifelong risk of ILR in prior studies, mostly tumor size, lymph vascular invasion, type of surgery and tumor margins, type of radiotherapy and adjuvant systemic therapies, and age at first breast cancer diagnosis [24, 31–34]. This analysis showed that the risk of ILR was associated mainly with the type of cancer-directed surgery and was not associated with the clinicopathological factors evaluated such as tumor size, grade, and lymphovascular invasion. Indeed, women undergoing breast-conserving surgery remained at higher risk of ILR compared to mastectomy despite the systematic use of chemotherapy and radiotherapy with or without endocrine therapy. Historical series have shown that radiotherapy and systemic therapy substantially decreases the rates of ILR after breast-conserving surgery [27, 28, 35]. For instance, in the National Surgical Breast and Bowel Project B-06 study, one of the largest phase III randomized trials studying the role of locoregional therapy in breast cancer outcomes, the

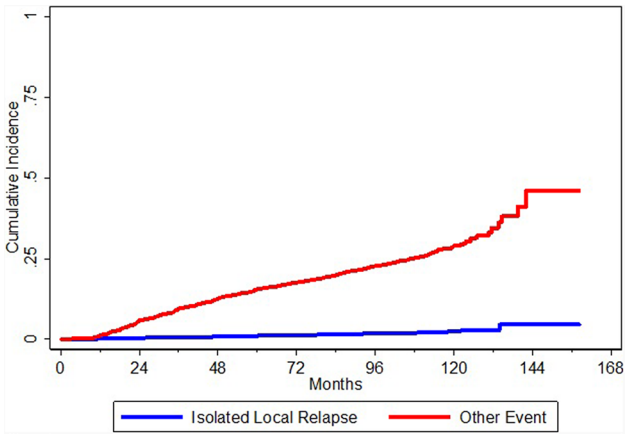

Fig. 2 Cumulative incidence of isolated local relapse and competing events including second malignancy, nodal recurrence, contralateral breast cancer, distant metastasis, and death

cumulative incidence of ILR over 20 years after lumpectomy was 14.3% among the women who received radiotherapy after lumpectomy and 39.2% among those who did not ($p < 0.001$) [36]. Similarly, adjuvant systemic therapies, combined with optimal local therapy, reduced the risk of locoregional failure by 20% at 5 years [37]. We found that women who did not receive adjuvant endocrine therapy were at greater risk of ILR. Tamoxifen was shown to decrease the risk of local recurrences even in breast cancer patients with favorable prognoses, such as node-negative, low-grade, and small tumors [38]. Moreover, aromatase inhibitors achieved a higher ILR-risk reduction over tamoxifen in postmenopausal women with early breast cancer [39]. This finding highlights the importance of an adequate adherence to endocrine therapy and comprehensive medication assessment to avoid deleterious interactions that may negatively affect the efficacy of endocrine therapy [40, 41].

Consistent with previous studies, we also found that younger women were at higher risk of developing ILR. Prior large series showed that women younger than 40 years are nearly twice as likely to develop long-life ILR as women older than 40 years [20, 42]. The prognostic impact of age on the risk of ILR can be, at least partly, explained by the unfavorable clinicopathological features of breast cancer in this specific subpopulation, such as larger tumor size, higher grade, and more frequent lymphovascular invasion [43, 44].

Table 2 Univariable analysis of isolated local relapse and competing events*

Patient and tumor characteristics		Isolated local relapse sHR (95% CI)	Competing events sHR (95% CI)*
Age§		0.96 (0.92–0.99)	0.99 (0.98–1.00)
Surgery	BCS	Reference	Reference
	Mastectomy	0.41 (0.21–0.82)	1.47 (1.27–1.71)
Tumor size	≤2 cm	Reference	Reference
	>2 cm	0.67 (0.39–1.15)	1.96 (1.69–2.28)
Lymph node involvement	1–3	Reference	Reference
	>3	1.21 (0.72–2.04)	2.36 (2.04–2.73)
Histological grade	I/II	Reference	Reference
	III	1.39 (0.81–2.40)	1.79 (1.53–2.09)
Estrogen receptor expression	Negative	Reference	Reference
	Positive	0.71 (0.26–1.95)	0.75 (0.55–1.02)
Progesterone receptor expression	Negative	Reference	Reference
	Positive	1.74 (0.75–4.04)	0.70 (0.58–0.84)
Histological subtype	Ductal	Reference	Reference
	Other	0.66 (0.33–1.35)	1.09 (0.92–1.30)
Adjuvant chemotherapy	3FEC-3D	Reference	Reference
	6ET	0.52 (0.25; 1.10)	0.65–0.52; 0.81)
	6FEC100	0.71 (0.36; 1.39)	0.80 (0.65; 0.98)
Number of chemotherapy cycles	6 cycles	Reference	Reference
	<6 cycles	0.92 (0.23; 3.77)	1.49 (1.08; 2.06)
Endocrine therapy	Yes	Reference	Reference
	No	4.20 (2.35; 7.5)	1.82 (1.44; 2.31)

BCS breast-conserving surgery, *C* cyclophosphamide, *D* docetaxel, *E* epirubicin, *F* 5-fluorouracil

*A competing event was defined by the occurrence of any breast cancer recurrence other than isolated local recurrence. It included nodal recurrences, distant recurrences, contralateral primary breast cancer, any second malignancy, and death from any cause without isolated local recurrence

§As continuous variable

Table 3 Multivariable analysis of isolated local relapse and competing events*

Patient and tumor characteristics		Isolated local relapse sHR (95% CI)	Competing event sHR (95% CI)*
Age§		0.95 (0.92–0.99)	0.99 (0.98–1.00)
Surgery	BCS	Reference	Reference
	Mastectomy	0.39 (0.17–0.86)	0.99 (0.83–1.18)
Tumor size	≤2 cm	Reference	Reference
	>2 cm	0.68 (0.37–1.24)	1.71 (1.43–2.02)
Lymph node involvement	1–3	Reference	Reference
	>3	1.73 (0.99–3.01)	2.16 (1.84–2.54)
Histological grade	I/II	Reference	Reference
	III	1.06 (0.50–2.23)	1.43 (1.11–1.84)
Progesterone receptor expression	Negative	Reference	Reference
	Positive	1.79 (0.70–4.58)	0.73 (0.59–0.89)
Adjuvant chemotherapy	3FEC-3D	Reference	Reference
	6ED	0.71 (0.31–1.60)	0.79 (0.61; 1.01)
	6FEC100	0.78 (0.37; 1.64)	0.91 (0.73; 1.15)
Number of chemotherapy cycles	6 cycles	Reference	Reference
	<6 cycles	1.42 (0.34; 5.87)	1.39 (0.96; 2.01)
Endocrine therapy	Yes	Reference	Reference
	No	2.73 (1.32; 5.67)	1.39 (0.96; 2.01)

BCS breast-conserving surgery, *C* cyclophosphamide, *D* docetaxel, *E* epirubicin, *F* 5-fluorouracil

*A competing event was defined by the occurrence of any breast cancer recurrence other than isolated local recurrence. It included nodal recurrences, distant recurrences, contralateral primary breast cancer, any second malignancy, and death from any cause without isolated local recurrence

§As continuous variable

It has been also hypothesized that multiple genomic and transcriptomic signaling pathways specifically activated in younger women with breast cancer can be associated with a poorer efficacy of local and systemic treatments [24, 45].

Although this study provides important insights on the recurrence pattern of HR + /HER2- BC with lymph node involvement from a prospective cohort of patients with histologically proven recurrences, several limitations should be acknowledged. Given that the follow-up duration in both PACS 01 and PACS 04 was 10 years, we could not collect long-term survival data in patients that experienced ILR and draw a conclusion on the impact of ILR on the risk of distant metastases and breast cancer-specific survival. Furthermore, the median follow-up of 9.1 years may be relatively short for defining the long-term risk of ILR, especially in women with HR + /HER2- BC; a longer follow-up would have been helpful to demonstrate whether the stable trend extends beyond 10 years. Another limitation is the lack of a clear definition of ILR in terms of true recurrences or new breast cancers. Traditionally, local relapses in the same quadrant with consistent histological subtype between the two tumors were considered local relapses. This definition categorized true recurrences and new primaries as 46% and 54%, respectively [46]. However, this definition has limitation due to possible misinterpretation of the anatomic site following breast conservative surgeries and differences in hormonal receptor expression between the primary and residual breast cancer after adjuvant therapies [47, 48]. High-throughput molecular analyses using genome/exome sequencing and copy number alteration analyses have shown higher concordance in comparing the local relapse and primary tumor [49–53]. Therefore, identifying patients with an increased risk of developing new primaries versus true recurrences would be beneficial for future studies to personalize adjuvant treatments after the primary tumor resection, such as determining the duration of endocrine therapy. Accurately distinguishing between true recurrences and new primaries among local recurrence cases would provide valuable important information for future studies to personalize the treatment of these patients. Last, this analysis could not include variables that are potentially associated with a higher risk of ILR, such as the presence of an extensive intraductal component in the primary tumor or mutations in breast cancer-related genes, mostly *BRCA*1 and 2 [31, 54].

Conclusion

As the understanding of the molecular biology of breast cancer and the impact of treatment advances continues to evolve, a constant reevaluation of relapsing patterns is required to optimize treatment strategies. This analysis

showed that the incidence of ILR in women with HR + / HER2- BC and lymph node involvement is low but remains constant over 10 years of follow-up. A more personalized long-term breast cancer surveillance in women at-risk of ILR and the development of genomic signatures for predicting ILR have the potential to impact long-term breast cancer outcomes.

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Author contributions BP: contributed to study concept and design. ER and BP: contributed to review of the literature, data analysis, and interpretation. TF: contributed to statistical analysis. All authors contributed to manuscript editing, critical review, and approval of the final version of this manuscript.

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Data availability Deidentified data can available to other researchers upon reasonable request and will be subject to the approval of a formal written data access request in accordance with Unicancer Data Access Policy and General Data Protection Regulation.

Declarations

Conflict of interest Thomas Filleron: consulting cellectis (My institution). Alessandro Viansone: Consulting/advisory: Seattle genetics; Speakers Bureau: None; Resaerch Funding: Pfizer; Travel, accommodation, and expenses: Eisai Europe. Mario Campone: Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: Novartis, Lilly; Participation on a Data Safety Monitoring Board or Advisory Board: Astra Zeneca, Novartis, Sanofi, Daiichi-Sankyo, Lilly, PET-Therapy, Menarini, Gilead, Seagen. Suzette Delaloge: Grants or contracts from AstraZeneca, Pfizer, Novartis, Roche Genentech, Lilly, Puma, Myriad, Orion, Amgen, Sanofi, MSD, BMS, Seagen, and Taiho; consulting fees from Isis/Servier, Cellectis, Pierre Fabre, and General Electric; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Seagen, AstraZeneca, Pfizer, Exact Sciences, Daiichi, and Lilly; support for attending meetings or travel from Pfizer, AstraZeneca, and Roche Genentech; and participation on a data safety monitoring board or advisory board for AstraZeneca, Sanofi, Orion, and Rappta. Barbara Pistilli: Consulting/Advisor: Puma Biotechnology, Novartis, Myriad Genetics, Pierre Fabre; Personal fees: Novartis, AstraZeneca, MSD Oncology, Pfizer; Research funding: Daiichi-Sankyo, Puma Biotechnology, Novartis, Merus, Pfizer, AstraZeneca. All other authors did report any conflict of interests regarding this manuscript.

Ethical approval The PACS 01 and 04 trials required a written informed consent signed by each patient before randomization. The studies were coordinated by the National French Cancer Centers Cooperative Group (UNICANCER), reviewed and approved by the ethics committee/institutional review board, and conducted according to the Declaration of Helsinki and European Good Clinical Practice requirements. The subgroup study did not require additional ethical approval.

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