

Risk factors for locoregional recurrence (LRR) after neoadjuvant chemotherapy: pooled analysis of prospective neoadjuvant breast cancer (BC) trials

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Background

LRR after neoadjuvant chemotherapy (NACT) for BC may impact patient's outcome. This study aimed to evaluate the rates of LRR as first event after NACT and to identify independent predictors of LRR.

Patients and Methods

A total of 10,075 women with primary BC and available follow-up from 9 prospective neoadjuvant trials (GeparDuo, GeparTrio pilot and main study, GeparQuattro, PREPARE, TECHNO, GeparQuinto, GeparSixto and GeparSepto) were included in this pooled analysis. The main endpoint was cumulative incidence rates of LRR as first event after NACT; distant recurrence, secondary malignancy or death was defined as competing event. Cumulative incidence of LRR was estimated according to the Gray's competing risk model¹. To identify predictors of LRR, surgery type, pathological complete response (pCR=ypT0 ypN0), BC subtypes (HR+/HER2-, HR+/HER2+, HR-/HER2+, TNBC) and other risk factors were evaluated using Fine-Gray's regression model². All analyses according to pCR were performed using landmark (landmark setting)³. The two-sided significance level was set to $\alpha=0.05$.

Results

Table 1. Baseline characteristics and response

Parameter	Category	N (valid %)	Parameter	Category	N (valid %)
Age, years	Median (range)	49 (21-80)	tumor grade	G1	336 (3.5)
cT	cT1	1195 (12.0)		G2	5037 (52.2)
	cT2	6277 (62.8)		G3	4279 (44.3)
	cT3	1425 (14.3)	BC subtypes	HR+/HER2-	3958 (45.8)
	cT4a-d	1102 (11.0)		HR+/HER2+	1458 (16.9)
cN	cN0	5098 (51.6)		HR-/HER2+	989 (11.5)
	cN1	4263 (43.2)		TNBC	2229 (25.8)
	cN2	385 (3.9)	Surgery type	BCS	6577 (68.1)
	cN3	133 (1.3)		Mastectomy	3080 (31.9)
Histological type	Ductal invasive	8150 (82.2)	pCR (ypT0 ypN0)	no	8020 (79.6)
	Lobular invasive	1039 (10.5)		yes	2055 (20.4)
	other	720 (7.3)			

Table 2: Multivariate analysis of LRRs, overall

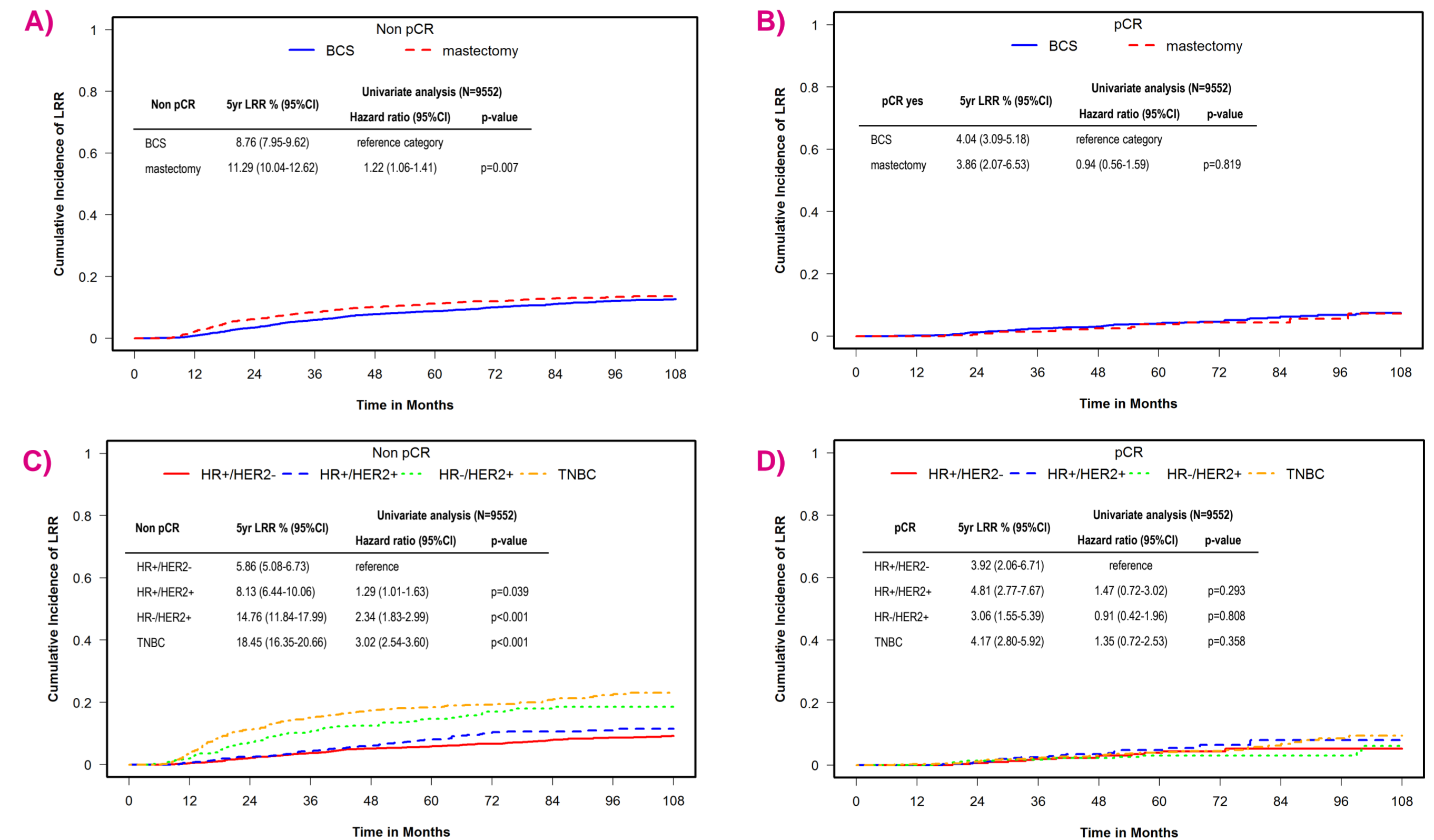
Parameter	Category	5-year LRR rate (95% CI)	Multivariate analysis (N=9552)	
			Hazard ratio (95% CI)	p-value
Age, years	>50	7.57 (6.77-8.42)	reference category	<0.001
	≤50	9.89 (9.07-10.75)	1.35 (1.16-1.57)	<0.001
cT	cT1-3	8.45 (7.85-9.08)	-	0.077
	cT4a-d	12.00 (10.06-14.12)	1.23 (0.98-1.55)	0.077
cN	negative	6.75 (6.04-7.51)	reference category	<0.001
	positive	11.18 (10.24-12.15)	1.47 (1.26-1.71)	<0.001
tumor grade	G1-2	6.91 (6.21-7.66)	reference category	0.001
	G3	11.38 (10.39-12.42)	1.33 (1.12-1.57)	0.001
Histological type	Ductal invasive	9.36 (8.70-10.04)	reference category	0.302
	Lobular invasive	5.47 (4.13-7.07)	0.789 (0.58-1.08)	0.135
	Other	8.69 (6.67-11.04)	0.92 (0.68-1.25)	0.613
BC subtypes	HR+/HER2-	5.99 (5.23-6.81)	reference category	<0.001
	HR+/HER2+	7.55 (6.13-9.15)	1.32 (1.04-1.67)	0.022
	HR-/HER2+	10.46 (8.51-12.63)	1.97 (1.50-2.59)	<0.001
	TNBC	14.41 (12.91-15.99)	2.72 (2.23-3.31)	<0.001
Surgery type	BCS	7.82 (7.15-8.53)	reference category	0.514
	Mastectomy	11.28 (10.13-12.50)	1.06 (0.89-1.25)	0.514
pCR (ypT0 ypN0) (landmark)	yes	4.07 (3.21-5.08)	reference category	<0.001
	no	9.52 (8.84-10.22)	3.33 (2.60-4.28)	<0.001

Table 3: Subgroup multivariate analysis by pCR

Parameter	Category	non-pCR patients		pCR patients	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age, years	>50	reference	0.001	reference	0.099
	≤50	1.32 (1.12-1.55)	0.001	1.52 (0.92-2.52)	0.099
cN	negative	reference	<0.001	reference	0.054
	positive	1.49 (1.27-1.74)	<0.001	1.61 (0.99-2.61)	0.054
tumor grade	G1-2	reference	<0.001	reference	0.971
	G3	1.39 (1.16-1.65)	<0.001	1.01 (0.62-1.64)	0.971
BC subtypes	HR+/HER2-	reference	<0.001	reference	0.314
	HR+/HER2+	1.23 (0.96-1.58)	0.097	2.12 (0.89-5.02)	0.089
	HR-/HER2+	2.05 (1.54-2.73)	<0.001	1.30 (0.56-3.03)	0.543
	TNBC	2.77 (2.27-3.39)	<0.001	1.65 (0.79-3.44)	0.180
Surgery type	BCS	reference	0.143	reference	0.464
	Mastectomy	1.13 (0.96-1.33)	0.143	0.78 (0.41-1.51)	0.464

Results

Figure 1: Cumulative incidence of LRR by pCR according to surgery type (A, B) and BC subtype (C, D)



- After a median follow-up in the entire cohort of 67 months (range 0-215 months), 959 (9.5%) LRRs as first event were observed.
- Age, clinical nodal status before NACT, tumor grade, pCR and BC subtypes but not surgery type were significant independent predictors of LRR in multivariate analysis (Table 2).
- Patients achieving a pCR have lower LRR rate compared to non-pCR. Patients treated with mastectomy and those with HR-/HER2+ or TNBC subtypes had higher LRR rates at 5 years in non-pCR subgroup only (Figure 1).
- In non-pCR subgroup age, tumor grade, HR-/HER2+ and TNBC subtypes were independent predictors of LRR whereas only cN+ showed a trend in predicting LRR in the pCR subgroup (Table 3).

Conclusions

- **Young age, node-positive and G3 tumors, non-pCR status, HER2+ and TNBC subtypes were found to significantly increase the risk of LRR as first event after NACT.**
- **Patients with HR-/HER2+ and TNBC not achieving pCR were at highest risk of LRR. Hence, there is a critical need to investigate better multimodality post-neoadjuvant therapies for this patients.**

References

1.Gray, R.J. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. The Ann Stat 1988; 16: 1141-1154; 2.Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. J Am Stat Assoc 1999; 94:496-509; 3.Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. J Clin Oncol 2013; 31:2963-9