



Locoregional risk assessment after neoadjuvant chemotherapy in patients with primary breast cancer: clinical utility of the CPS + EG score

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Abstract

Purpose Locoregional control is a prerequisite to cure primary breast cancer but the prediction of locoregional recurrence to guide further local therapy following neoadjuvant chemotherapy remains a challenge. The CPS + EG score was designed to predict distant recurrences. Here we examine its ability to predict both not only distant but also locoregional recurrences with respect to accuracy and clinical applicability.

Methods Clinical data from 432 patients with primary breast cancer treated with neoadjuvant chemotherapy between 2003 and 2011 were prospectively collected. Using the Kaplan–Meier method we analyzed the risk of local and distant recurrences according to individual CPS + EG scores, stratified by type of surgery. Possible confounding of the relationship between recurrence risk and CPS + EG score by established risk factors was accounted for in multiple survival regression models. Additionally, we analyzed the performance of the CPS + EG score to predict isolated locoregional recurrence by censoring patients with prior or simultaneous distant metastases.

Results 5-year locoregional recurrence-free survival was 90%, and 5-year distant metastases-free survival was 82%. The CPS + EG score stratified patients into six prognostic groups with distinct 5-year locoregional recurrence-free survival, ranging from 100 to 41% ($p=0.02$) and 5-year distant metastases-free survival, ranging from 96 to 35% ($p<0.0001$). 8 patients (17%) with CPS + EG scores ≥ 4 experienced locoregional recurrence—5 of them presented with simultaneous distant disease.

Conclusion The CPS + EG score, originally designed to predict distant relapse, is also valuable for assessing local recurrence risks. Our data demonstrate that distant and locoregional recurrence risks are closely related. As prognosis of patients with high risk of locoregional failure based on CPS + EG is dominated by distant recurrences, escalating local therapies may have limited impact on overall prognosis.

Keywords Primary breast cancer · Prognostic index · Neoadjuvant chemotherapy · CPS + EG score

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Introduction

Neoadjuvant chemotherapy (NAC) has become a standard of care for patients with primary breast cancer (PBC) with a clear indication for chemotherapy [1]. NAC offers several advantages: it increases breast conservation rates, reduces rate of axillary lymph node dissection, and allows in vivo assessment of tumor response to treatment [2, 3]. By combining neoadjuvant chemotherapy with HER2-targeted agents, pathologic complete response (pCR) rates of up to 40–80% can be achieved [4–6]. pCR is strongly associated with superior distant metastases-free survival (DMFS) and overall survival (OS) in the hormone receptor-negative subgroups [3, 7, 8]. In hormone receptor (HR) positive, luminal subtypes the association between pCR and survival is less pronounced, mainly because pCR rates are low and many patients who do not achieve a pCR still have a favorable prognosis in part due to the effect of adjuvant endocrine therapy [8, 9].

Locoregional recurrence (LRR) is associated with increased risk of distant recurrence leading to poor overall survival. Therefore, locoregional control is an important goal in breast cancer therapy [10, 11]. It is essential to identify patients at high risk of LRR that might benefit from more radical locoregional treatment (e.g., mastectomy (ME) or extended radiation fields) but at the same time to avoid overtreatment and potentially de-escalate therapy for those with minimal risk. Several predictive factors have been described to identify such patients in the neoadjuvant setting [12–15].

We recently evaluated prediction accuracy and clinical applicability of the MD Anderson Prognostic index (MDAPI) in 456 patients treated in our institution between 2003 and 2011 [16]. The MDAPI was originally published by Chen et al. in 2005 to identify patients with breast conserving therapy (BCT) that may benefit from an extended local therapy. The score is composed of clinical nodal status, residual pathologic tumor size, pattern of residual disease, and lymphovascular space invasion in the surgical specimen [12]. In our previous work, we could however not confirm a clinical utility of the MDAPI to guide local therapy in patients with PBC [16]. This was mainly due to low numbers of patients in the high-risk category as well as the competing risk of distant metastasis (DM) dominating prognosis in these patients. Interestingly, MDAPI led to a more distinct stratification of DM than of LRR. Our data demonstrate that prediction of local recurrences is strongly influenced by factors also predicting DM.

Based on these results, we wanted to evaluate a prognostic score originally trained to predict distant rather than local recurrences for prediction of locoregional failure.

Recently, a scoring system, based on pre-treatment clinical stage (CS), post-treatment pathologic stage (PS), estrogen receptor status (E), and tumor grade (G), the CPS + EG score, has been demonstrated to allow a more refined risk stratification for distant metastases-free survival (DMFS) [17–19]. It allocates patients to seven groups with distinct 5-year DMFS and disease-free survival (DFS) rates. This score has been successfully validated and constitutes a central inclusion criterion for a post-neoadjuvant trial in HR+ breast cancer (PenelopeB; NCT 01864746) [8, 18–20].

Interestingly, it was recently suggested that the CPS + EG score, though originally designed to predict DMFS, can also stratify patients with respect to LRR [21].

The study by Vila et al., however, did not take into account the temporal context of LRR and DM. LRRs were counted as events regardless of whether they occurred isolated or concomitantly with DM. The role of LRR with simultaneous DM is not fully understood. It remains unclear whether LRR can be seen as the origin of DM or if they develop simultaneously or both [22–24]. If LRR is seen as an indicator, the prevention of LRR by adapting local therapy is only important if it occurs as an isolated event and not in the context of a simultaneous distant recurrence which will otherwise dominate therapy and prognosis.

In our present study, we investigate the ability of the CPS + EG score to stratify patients with respect to local and distant disease. Additionally, we examine its ability to identify patients with LRR, focusing on LRR as the first site of recurrence.

Materials and methods

Patients

Patient and tumor characteristics, therapy, and follow-up of all patients referred to the Heidelberg certified breast cancer unit for diagnosis and treatment of PBC have been prospectively documented in our database since January 1st, 2003. All patients gave informed consent on the use of demographic and treatment data. To ensure a follow-up of at least 5 years, we excluded all patients that were diagnosed after 2011. We also excluded all patients with DM, non-invasive, bilateral, recurrent or inflammatory disease, or incomplete therapy (R1 resection, incomplete axillary staging, less than 50% of the planned chemotherapy, refusal of radiotherapy) (Fig. 1).

Diagnostic and therapeutic procedures

Patients were assessed at presentation using physical examination, ultrasound of the breast and regional lymphatic nodes, and mammography. Patients were diagnosed by core

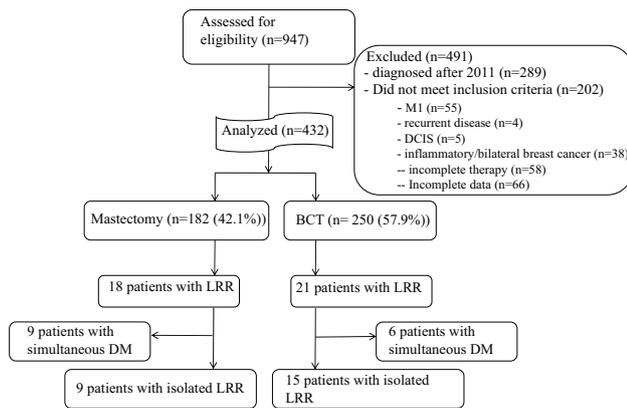


Fig. 1 CONSORT diagram

needle biopsy to provide information on histological type, HR and HER2 status. Tumors were classified according to the St. Gallen surrogate definition for intrinsic subtypes [1, 25]: Luminal A (hormone receptor (HR) positive, HER2 negative, Ki67 < 20%), Luminal B/HER2 negative (HR positive, Ki67 \geq 20%), Luminal B/HER2 positive (HR positive, Her2 positive), HER2 positive/non-luminal (HR negative, HER2 positive), and triple negative [1, 25].

DM were excluded by imaging. Clinical stage was determined according to the 6th edition of the American Joint Committee on Cancer Breast Cancer Staging System.

Chemotherapy regimens followed our institutional protocols and were anthracycline- and/or taxane-based. Patients treated before the approval of trastuzumab in 2006 (12.4%) did not receive (neo)adjuvant trastuzumab. Surgery was performed within four weeks after chemotherapy. Patients with clinically node-negative disease underwent sentinel lymph node biopsy before NAC. Patients with involved sentinel nodes or clinically node-positive disease received complete axillary dissection at the time of the breast surgery. Pathological complete response was defined as no residual invasive cancer in the breast and lymph nodes.

Statistical methods

The CPS-EG score was calculated for all patients as previously described, resulting in seven prognostic subgroups [17]. Patients were stratified into 3 risk groups: low-risk (0 and 1), intermediate-risk (2 and 3), high-risk (4, 5 and 6).

We performed uni- and multivariate analysis of the entire cohort and stratified by type of surgery (BCT/ME) to validate the prognostic performance of the CPS + EG score. LR was defined as recurrence within the ipsilateral breast or thoracic wall. LRR was defined as ipsilateral recurrence within the breast, the thoracic wall, or the axillary lymph nodes. To test the clinical utility of CPS + EG score, LRR estimates were calculated by 1.) counting LRR as an event regardless

if it was the only or first site of recurrence, and 2.) censoring patients at the time of diagnosis of DM if these occurred prior, at the same time or within up to 3 months after LRR.

Time to LR, LRR, or DM was calculated from the start of chemotherapy to local, locoregional, or distant recurrence, respectively. Survival times of patients who were alive and did not experience a specific event (locoregional, local, or distant recurrences) at last follow-up were considered censored.

Kaplan–Meier curves, log-rank tests, and univariate survival regression models were used to investigate the association between the risk of recurrence and CPS + EG score, for all patients and stratified by type of surgery (BCT vs. ME). Multiple survival regression analyses were conducted to adjust for the possible confounding effects of established prognostic factors. All statistical tests were two-sided and probability values smaller than 0.05 were considered statistically significant. Statistical analyses were conducted using SAS version 9.4 and survival curves were drawn using the R software environment for statistical computing.

Results

Our previous work included 456 patients treated between 2003 and 2011 in our department [16]. The CPS + EG score could be calculated for 438 of them. 6 patients were excluded from the analysis as no follow-up was available so that 432 patients were included into the present study (Fig. 1).

Patient and tumor characteristics stratified by type of surgery are summarized in Table 1. The median age at diagnosis was 48 years (range 20–74 years). 28.0% of tumors were triple negative, 28.0% were luminal B-like (Her2 negative), 14.6% luminal A-like, 12.0% Her2 positive (non-luminal), and 11.6% were luminal B (Her2 positive). In 5.8% no categorization was possible.

72.5% of patients had stage II, 24.1% stage III, and only 3.5% stage I disease. 250 patients (57.9%) were definitively treated with BCT and 182 (42.1%) with ME.

22.5% of patients achieved a pCR (ypT0/is ypN0). pCR rates were highest in luminal B/HER2 positive (46.0%) and HER2 positive/non-luminal tumors (42.3%) and lowest in luminal A-like tumors (3.2%).

All patients treated with BCT received adjuvant radiotherapy to the breast with tangential fields. 81.3% of mastectomized patients received radiotherapy to the chest wall and 44.4% of all patients received radiotherapy to the regional lymph nodes.

The distribution of CPS + EG scores is presented in Table 1. Most of the 432 patients presented with a CPS + EG score of 2 (37%), while only 3 patients (0.7%) had a score of 5 and none higher. Due to low patient numbers and event

Table 1 Main patient and tumor characteristics in the investigated collective, and differences by surgical procedure

Variable	Level	Patients	BET	%	ME	%	<i>p</i> value
Age	–41	118	57	22.8	61	33.5	0.09
	42–47	100	62	24.8	38	20.9	
	48–56	111	66	26.4	45	24.7	
	57+	103	65	26.0	38	20.8	
cT	0–1	31	19	7.6	12	6.6	< 0.0001
	2	291	197	78.8	94	51.7	
	3	85	28	11.2	57	31.3	
	4	25	6	2.4	19	10.4	
cN	0	184	124	49.6	60	33.0	0.004
	1	217	113	45.2	104	57.1	
	2	12	6	2.4	6	3.3	
	3	19	7	2.8	12	6.6	
AJCC-CS	IA	15	8	3.2	7	3.9	< 0.0001
	IIA	151	107	42.8	44	24.2	
	IIB	162	102	40.8	60	33.0	
	IIIA	65	20	8.0	45	24.7	
	IIIB	20	6	2.4	14	7.7	
	IIIC	19	7	2.8	12	6.6	
Mol. ST	Her2	52	28	11.2	24	13.2	0.09
	LmA	63	34	13.6	29	15.9	
	LmBneg	121	63	25.2	58	31.9	
	LmBpos	50	28	11.2	22	12.1	
	TNBC	121	84	33.6	37	20.3	
	Unknown	25	13	5.2	12	6.6	
Grading	1	8	6	2.4	2	1.1	0.001
	2	189	91	36.4	98	53.9	
	3	235	153	61.2	82	45.1	
ER	0	173	112	44.8	61	33.5	0.02
	1	259	138	55.2	121	66.5	
PR	0	213	140	56.0	73	40.1	0.001
	1	219	110	44.0	109	59.9	
Her2	0	329	193	77.5	136	74.7	0.50
	1	102	56	22.5	46	25.3	
Ki67%	0–25	146	81	32.4	65	35.7	0.24
	26–50	105	55	22.0	50	27.5	
	51–75	56	33	13.2	23	12.6	
	76–100	66	46	18.4	20	11.0	
	Unknown	59	35	14.0	24	13.2	
ypT	0	111	80	32.5	31	17.0	< 0.0001
	1	173	108	43.9	65	35.7	
	2	89	43	17.5	46	25.3	
	3	30	2	0.8	28	15.4	
	4	3	1	0.4	2	1.1	
ypN	is	22	12	4.9	10	5.5	< 0.0001
	0	231	149	69.3	82	48.2	
	1	100	57	26.5	43	25.3	
	2	38	6	2.8	32	18.8	
	3	16	3	1.4	13	7.7	

Table 1 (continued)

Variable	Level	Patients	BET	%	ME	%	<i>p</i> value
AJCC-PS	0	126	87	34.8	39	21.4	< 0.0001
	IA	112	75	30.0	37	20.3	
	IB	10	6	2.4	4	2.2	
	IIA	84	57	22.8	27	14.8	
	IIB	34	13	5.2	21	11.5	
	IIIA	48	8	3.2	40	22.0	
	IIIB	2	1	0.4	1	0.6	
	IIIC	16	3	1.2	13	7.1	
pCR	0	306	163	65.2	151	83.0	< 0.0001
	1	126	87	34.8	31	17.0	
L-status	0	355	221	88.4	134	73.6	< 0.0001
	1	77	29	11.6	48	26.4	
Multifocal	0	360	222	88.8	138	75.8	< 0.0001
	1	72	28	11.2	44	24.2	
CPS + EG	0	39	30	12.0	9	5.0	0.17
	1	78	48	19.2	30	16.5	
	2	160	91	36.4	69	37.9	
	3	108	58	23.2	50	27.5	
	4	44	21	8.4	23	12.6	
	5	3	2	0.8	1	0.6	
	6	0	0	0	0	0	

Bold represents probability values under 0.05

AJCC-CS American Joint Committee on Cancer (AJCC)-clinical stage, *Mol.ST* molecular subtype, *ER* estrogen receptor, *PR* progesterone receptor, *AJCC-PS* AJCC-pathological stage

counts in some of the CPS + EG score groups, we stratified patients into 3 risk groups: 27% of patients were classified as low-risk (CPS + EG 0 and 1), 62% as intermediate-risk (CPS + EG 2 and 3) and 11% as high-risk (CPS + EG 4, 5 and 6).

There were no significant differences in the distribution of CPS + EG scores between BCT and mastectomized patients ($p=0.17$) (Table 1).

Interestingly, mastectomized patients without radiation had significantly lower CPS + EG scores compared to patients with postmastectomy radiation: CPS + EG 0 and 1: 47% vs. 15.5%; CPS + EG ≥ 4 2.9% vs. 15.5% ($p=0.0006$) (Table 2).

Within the median follow-up of 59 months (range 6–142 months) LR was observed in 26 patients (6.0%). 39 patients (9%) experienced LRR and 87 patients (20.1%) presented with DM. In 15 out of 39 patients LRR was diagnosed after or simultaneously (within 3 months) with the diagnosis of distant metastases. Among the 24 patients (5.6%) who developed isolated LRR 15 occurred in patients with BCT (6.0% of all BCT patients) and 9 in mastectomized patients (4.9% of all ME patients) (Fig. 1).

To evaluate the local risk of recurrence, we calculated 5-year LR-free survival (LRFS) rates as well as 5-year LRR-free survival (LRRFS) rates stratified by surgical

Table 2 Mastectomized patients stratified after postmastectomy radiation and CPS + EG score

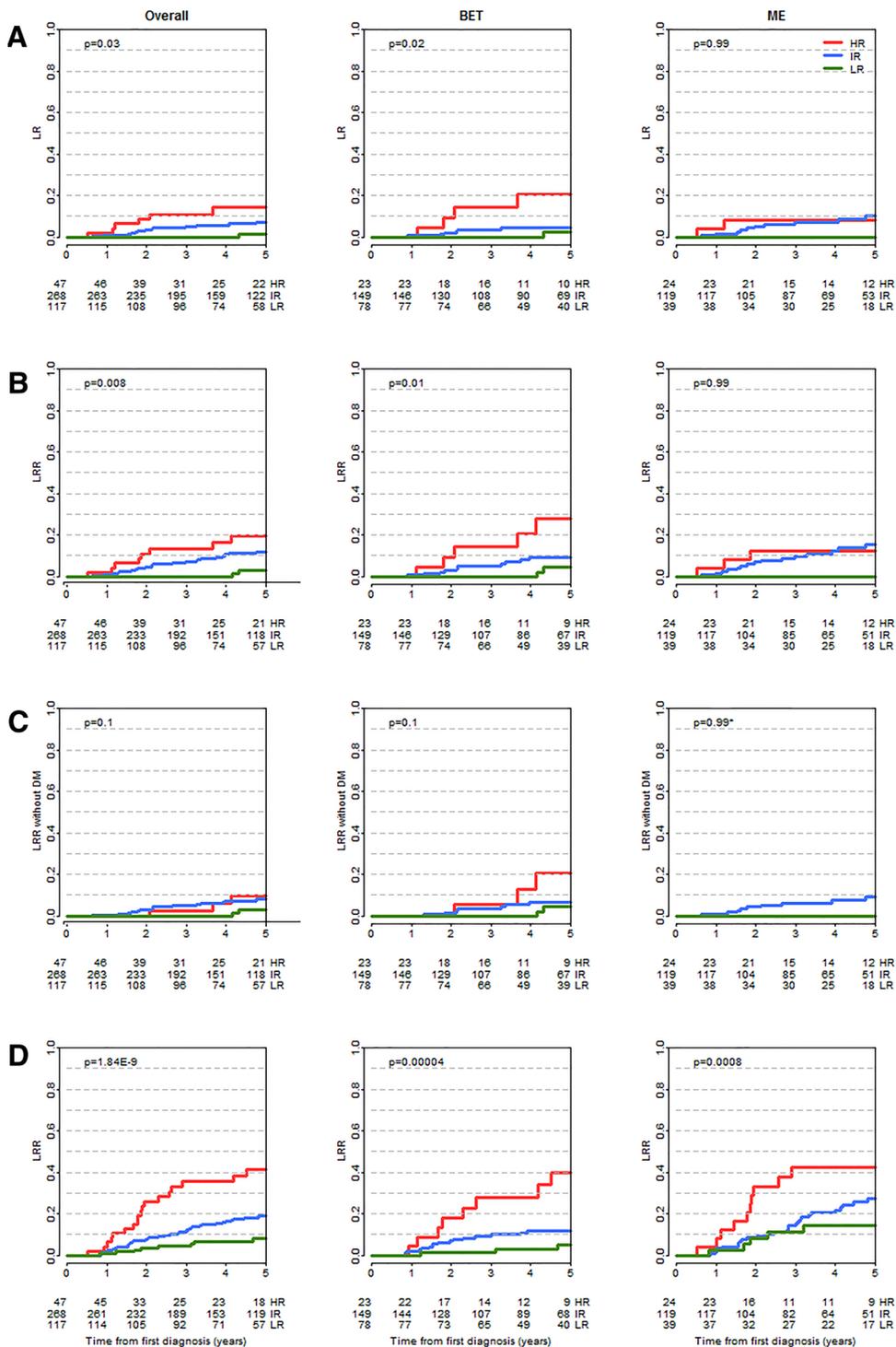
CPS + EG	Patients	ME without radiation	%	LRRw/oDM	ME + radiation	%	LRRw/oDM	<i>p</i> value
0	9	6	17.6	0	3	2.0	0	0.0006
1	30	10	29.4	0	20	13.5	0	
2	69	12	35.3	2	57	38.5	3	
3	50	5	14.7	0	45	30.4	4	
4	23	1	2.9	0	22	14.9	0	
5	1	0	0	0	1	0.7	0	
6	0	0	0	–	0	0	–	

procedure (BCT/ME). Kaplan–Meier curves for LR are shown in Fig. 2a.

The overall 5-year LRFS rate was 94% (95% CI 91% to 96%). The CPS + EG score stratified the overall and BCT group into three prognostic groups with clearly distinct 5-year LRFS rates, of 99%, 93%, 86% (overall group; $p=0.03$) and 99%, 95%, 81% (BCT; $p=0.02$), respectively.

Patient numbers and event counts in the mastectomized group were low. Within the ME group 12 local recurrences occurred, none of which in the low-risk group ($n=39$), 2 in the high-risk group ($n=24$) and 10 in the intermediate-risk group ($n=119$) ($p=0.99$). No differences in 5-year LRFS rates were observed between the BCT and ME group (Online Resource 1A).

Fig. 2 Kaplan-Meier curves for LR (a), LRR (b), LRRw/oDM (c) and DM (d) stratified by CPS + EG score groups and surgical procedure (BCT/ME). *Overlapping curves for the IR and LR groups



Kaplan–Meier curves for LRR irrespective of previous or synchronous DM are shown in Fig. 2b.

The CPS + EG score stratified the overall patient cohort and patients with BCT into three groups with clearly distinct 5-year LRRFS rates of 98%, 88%, and 80% in the overall group ($p=0.008$) and 97%, 90%, and 74% in the BCT group ($p=0.01$).

The CPS + EG score failed to stratify mastectomized patients into prognostic LRR-risk groups (Online Resource 1B).

To evaluate the risk of DM, we calculated 5-year DMFS rates stratified by surgical procedure. Kaplan–Meier curves for DM rates are shown in Fig. 2d.

The CPS + EG score correlated with 5-year DMFS rates in the overall group as well as in patients with BCT and ME (overall: low: 93%, intermediate: 82%, high-risk: 52%; $p < 0.0001$; BCT: low: 97%, intermediate: 87%, high-risk: 61%; $p < 0.0001$; ME: low: 84%, intermediate: 76%, high-risk: 46%; $p = 0.0008$, respectively). Mastectomized patients were at higher risk of DM compared to patients with BCT irrespective of their CPS + EG risk category (overall group: ME 27% vs. BET 13%, CPS-EG low-risk: 16% vs. 3%; intermediate-risk: 24% vs. 13%; high-risk: 54% vs. 39%) (Online Resource 1D). This clearly suggests that factors determining the type of surgery, not contained within the CPS + EG score, have additional prognostic value.

Although the CPS + EG score was originally designed to predict DM we intended to analyze its reliability to identify cases of isolated LRR. We therefore calculated 5-year LRRFS rates excluding patients with previous or

simultaneous occurrence of DM (LRRw/oDM). In this context, only LRR as first event (at least 3 months interval to the diagnosis of distant metastases) were counted as an event. Kaplan–Meier curves for LRRw/oDM are shown in Fig. 2c. 39 out of 432 patients presented with LRR but only 24 of them had isolated LRR.

The CPS + EG score failed to stratify patients into groups with distinct 5-year LRRw/oDM-free survival rates.

Only 3 out of 24 LRRw/oDM events occurred in the high-risk group. 5 out of 8 LRR events in the high-risk group occurred simultaneously with or after DM (Online Resource 1C). Interestingly, all three LRRw/oDM events within the high-risk group occurred in BCT patients.

Univariate survival analyses for the overall group revealed that ER status, lymph node status, and multifocal lesions were associated with LRR-risk (Table 3). Multifocal lesions were also associated with LRRw/oDM-risk (Online Resource 2).

Adjustment for possible confounding effects confirmed an independent association between the CPS + EG score and LRR-risk ($p=0.01$, Table 3) as well as LRRw/oDM-risk ($p=0.004$, Online Resource 2).

Discussion

Neoadjuvant chemotherapy is a standard for patients with a clear indication for chemotherapy. Nevertheless, the identification of patients with high risk of locoregional recurrence remains a challenge. We have recently analyzed the MDAPI

Table 3 Results from univariate and multiple survival analyses on LRR

Variable	Level	Patients	Events	Univariate				Multiple			
				HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value		
Age	–41	118	18	Ref.			0.05	Ref.			0.12
	42–47	100	9	0.60	0.27	1.34		0.62	0.27	1.44	
	48–56	111	8	0.50	0.22	1.16		0.60	0.25	1.40	
	57+	103	4	0.24	0.08	0.72		0.27	0.09	0.82	
ER	0	173	20	Ref.			0.04				
	1	259	19	0.52	0.28	0.97					
L-status	0	355	26	Ref.			0.01				
	1	77	13	2.39	1.22	4.66					
Multifocal	0	360	28	Ref.			0.03	Ref.			0.01
	1	72	11	2.14	1.06	4.31		2.50	1.20	5.20	
CPS + EG	0	39	0	–	–	–	0.02	–	–	–	0.01
	1	78	2	0.18	0.04	0.81		0.20	0.04	0.87	
	2	160	14	0.65	0.31	1.34		0.74	0.36	1.55	
	3	108	15	Ref.				Ref.			
	4	44	6	1.08	0.42	2.79		1.20	0.45	3.17	
	5	3	2	5.43	1.24	23.8		8.25	1.80	37.9	

Bold represents probability values under 0.05

HR hazard ratio, CI confidence interval, ER estrogen receptor

score for its ability to guide locoregional therapy but were unable to demonstrate clinical utility [16].

The CPS + EG score offers several advantages: while the MDAPI is determined by factors reflecting the extent of local expansion and neglects tumor biology, the CPS + EG score also takes into account grade and HR status. High tumor grade and negative HR status are known to be strongly associated with LRR, so a score predicting LRR should account for these factors [15, 17, 26]. Though the CPS + EG score was initially designed to predict DM a recent publication suggested that it might also be able to predict locoregional disease [21]. We therefore decided to evaluate the performance of the CPS + EG score in our patient cohort.

The CPS + EG score was able to stratify the overall and BET patients cohort according to local-, locoregional-, and distant disease recurrence risk. Within the ME group, the CPS + EG score stratified patients according to distant disease recurrence but failed to discriminate patients according to local- and locoregional recurrence risk.

Compared to the initial reports we observe a shift to lower CPS + EG scores: most patients presented with CPS + EG scores of 2 (our cohort: 37%; Jeruss et al.: 26.3%) and only few patients obtained a CPS + EG Score of ≥ 5 (our cohort: 0.7%; Jeruss et al.: 6.4%) [17]. This most likely reflects the change of use of neoadjuvant chemotherapy over time as our cohort was treated between 2003 and 2011 whereas the cohort of Jeruss et al. comprises the years 1997–2003. Initially NACT was used mostly for advanced or inoperable breast cancer but nowadays is also given to patients with smaller operable tumors. In addition, more effective therapies (including HER2 targeted agents) and better selection of patients might have influenced pCR rates and pathologic stage which is important for the CPS + EG score. Accordingly, 29.2% of our patient cohort presented with AJCC-PS 0 vs. 14.0% of the initial cohort [17]. Patients receiving neoadjuvant trastuzumab were excluded in the initial and validation cohort [17, 18], which might have contributed to this difference. Marmé et al. validated the CPS + EG score in a more recent cohort, including patients with neoadjuvant trastuzumab [19]. Group distribution and AJCC-PS stages were similar compared to our results with 31.4% of patients presenting with a CPS + EG score of 2 and 25.4% presenting with AJCC-PS 0 [19].

In contrast to the MDAPI as previously reported by our group, the CPS + EG score was not associated with the surgical approach but instead with postmastectomy radiotherapy. Patients not receiving postmastectomy irradiation had significantly lower CPS + EG scores compared to patients with postmastectomy radiation. Due to low patient numbers and event rates in the high-risk group we were unable to address the question whether postmastectomy irradiation could potentially reduce the risk of LRRw/oDM in patients with high CPS + EG scores, formally.

It was recently suggested by Vila et al. that the CPS + EG score might be as useful tool to select mastectomized patients for postmastectomy radiation therapy [21]. As in previous studies the authors counted LRRs as an event regardless of whether this was the first site of recurrence or occurred concomitant with or after distant disease.

The prevention of local failure likely is of little benefit for those patients with simultaneous DM, which will in these cases dictate therapy and prognosis.

In the present study we additionally analyzed patients with isolated LRR, not counting events when DM were diagnosed before, simultaneously or within 3 months after diagnosis of LRR.

Almost half of the patients that presented with LRR were simultaneously diagnosed with DM. Only 3 out of 24 LRRw/oDM events occurred in the high-risk CPS + EG group. Interestingly all LRRw/oDM events in the high-risk group were observed in patients with BET.

Overall, LRRw/oDM rates were similar in patients with BET (6.0%) and ME (4.9%) as well as in mastectomized patients with (4.7%) and without radiotherapy (5.9%). Nevertheless, therapeutic consequences that might be drawn from this observation depend on the role of LRR in patients with simultaneous DD: if LRR gave rise to distant metastases, escalating local therapy (surgical strategies or radiotherapy) might be an effective way to prevent metastases in these patients. Metastases that arise in parallel and independently from LRR (e.g., from micrometastases or circulating tumor cells) could not be prevented by escalating local therapy. These patients might rather benefit from post-neoadjuvant systemic therapy [27].

Whether LRR can be seen as a marker or as cause of DM is still discussed controversially and not completely clear. Possibly both models could apply in parallel. Several studies have tried to address this question with different results [23, 24, 28, 29].

In conclusion, our study shows that the CPS + EG score can stratify patients with respect to both, LRR as well as DM risk. However, it remains difficult to distinguish between the risk of local and distant failure since disease recurrence at both sites is inherently correlated. This limits the utility of the CPS + EG and other scores predicting local recurrences to guide local therapy. Scoring systems that enable better discrimination of local and distant disease recurrence risks would be needed but seem difficult to develop. In addition, as prognostic multigene assays are being used more widely in routine clinical practice, these should be included once follow-up of such cohorts is long enough.

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AS, CS: data acquisition; FM: study conception, data analysis, writing of the manuscript, supervision of the work.

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Compliance with ethical standards

Conflict of interest Laura Michel has received a research grant from the Medical Faculty of the University of Heidelberg; Laura Sommer, Rosa González Silos, Michael Golatte, Jörg Heil, André Henigs, Julia Seitz, Katharina Smetanay and Christof Sohn declare that they have no conflict of interest; Justo Lorenzo Bermejo has received personal fees from Roche and the Diabetes Institut Heidelberg as well as funding from the European Union, DFG and BMBF; Alexandra von Au has received a research grant from the Medical Faculty of the University of Heidelberg; Florian Schütz has received remuneration from AstraZeneca, Amgen, MSD, Novartis and has had consultant/advisory role for Roche, Pfizer and Lilly; Andreas Schneeweiss reports grants from Celgene, Roche, AbbVie, Molecular Partner, personal fees from Roche, AstraZeneca, Celgene, Roche, Celgene, Pfizer, AstraZeneca, Novartis, MSD, Tesaro, Lilly, Pfizer; Christof Sohn: data acquisition; Frederik Marmé has received remuneration from Roche, Amgen, Clovis, AstraZeneca, Pfizer, Novartis and has had consultant/advisory role for ParmaMa, Tesaro, Celgene, Eisai, Curevac, GenomicHealth.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Human and animals rights This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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