Breast Cancer Research and Treatment
https://doi.org/10.1007/s10549-022-06680-7

PRECLINICAL STUDY

The clinical relevance of various methods of classifying ipsilateral breast tumour recurrence as either true local recurrence or new primary

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Received: 15 January 2022 / Accepted: 6 July 2022

Abstract

Purpose Describes the relevance of –various classification methods for ipsilateral breast tumour recurrence (IBTR) as either true recurrence (TR) or new primary (NP) on both disease-specific survival (DSS) and distant metastasis-free survival (DMFS).

Method Two hundred and thirty-four of 4359 women undergoing breast-conserving therapy experienced IBTR. We compared the impact of four known classification methods and two newly created classification methods.

Results For three of the methods, a better DSS was observed for NP compared to TR with the hazard ratio (HR) ranging from 0.5 to 0.6. The new Twente method classification, comprising all classification criteria of three known methods, and the new Morphology method, using only morphological criteria, had the best HR and confidence interval with a HR 0.5 (95% CI 0.2–1.0) and a HR 0.5 (95% CI 0.3–1.1), respectively. For DMFS, the HR for NP compared to TR ranged from 0.6 to 0.9 for all six methods. The new Morphology method and the Twente method noted the best HR and confidence intervals with a HR 0.6 (95% CI 0.3–1.1) and a HR 0.6 (95% CI 0.4–1.2), respectively.

Conclusion IBTR classified as TR or NP has a prognostic value for both DSS and DMFS, but depends on the classification method used. Developing and validating a generally accepted form of classification are imperative for using TR and NP in clinical practice.

Keywords Ipsilateral breast tumour recurrence · True recurrence · New primary

Introduction

For early-stage breast cancer, breast-conserving therapy (BCT) is currently considered the treatment of choice. Following BCT, any ipsilateral breast tumour recurrences (IBTR) can be diagnosed shortly after initial treatment but also many years later.

Studies have identified IBTR as an independent predictor of distant metastases and survival [1–4]. Fisher et al. noted from 9-year follow-up data a threefold greater risk of distant metastases for cases diagnosed by IBTR after BCT when compared to those without IBTR [5]. Wapnir et al. in a large study with a median study time of 13.3 years noted that IBTR was a reliable indicator of worse distant metastasis-free survival (DMFS) at the 5-year point after IBTR [6].

In addition, time from initial breast cancer treatment until the occurrence of IBTR has been identified by other researchers as a prognostic factor for disease-specific survival (DSS) and DMFS [3, 6–9]. A short IBTR interval was

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Published online: 08 August 2022

found to be a strong determinant of the risk of distant metastases. From this, it was postulated that early IBTR and late IBTR may correspond to two distinct types of IBTR: (a) true recurrence (TR), corresponding to regrowth of resistant cells after initial treatment and (b) new primary (NP), corresponding to new cancer growth [10–14]. One relevant question in interpreting the clinical relevance of IBTR concerns the discrimination between TR and NP. Studies have used various methods of classifying IBTR into TR and NP [10–13]. However, no generally accepted classification of TR and NP yet exists. This is unsatisfactory when assessing the relevance of TR and NP to outcomes in daily practice.

Therefore, we concluded that it is vital to assess the prognostic value of IBTR, classified as TR or NP.

In the present large population-based, single-centre study, we performed an explorative analyses to assess the value of classifying IBTR (as first event) into TR or NP, by comparing several classifications methods. We focussed on DSS and distant metastasis-free survival (DMFS). We used four known methods from the literature, namely those of Huang, Yi, Panet-Raymond, and Komoike, plus two self-created new classification methods [10–13].

Patients and methods

We reviewed the records of 4929 women diagnosed with invasive breast cancer in our region between 1985 and 2015, all treated by BCT. All the women in our region had received their radiotherapy at the Radiotherapy Department of Medisch Spectrum Twente, Enschede, the Netherlands. All patient data, including demographics, histology, staging information, treatment, and outcome, had been recorded and updated regularly. Histological examinations were carried out at the Pathology Laboratory Oost Nederland. Tumours were classified according to the TNM classification of the UICC, 7th edition 2009.

IBTR was defined as a recurrence of invasive carcinoma that is localized in the ipsilateral breast. Patients were re-staged after the diagnosis. An IBTR as a first event was assumed to be an IBTR without distant metastases and/or regional recurrence, before, simultaneously or within one months after diagnosis of IBTR.

Involvement of the margins of lumpectomy specimens were considered to indicate the presence of microscopic involvement of invasive carcinoma in the inked edges of the lumpectomy specimen.

Patient selection

To exclude any interference from a second contra-lateral breast cancer, we restricted ourselves to those women with unilateral breast cancer, leaving 4414 women. During the study period of over thirty years, 289 IBTR cases were identified. Seven patients developed their IBTR after having developed DM, whilst in 37 cases of IBTR this occurred simultaneously or within 1 month after diagnosis of IBTR metastases. All those cases were excluded. Finally, we excluded six cases of IBTR that showed simultaneous occurrence of regional recurrences and five cases in which an IBTR occurred after a regional recurrence. This resulted in a cohort of 4,359 women leading to 234 IBTR cases, diagnosed as first event.

The 234 IBTR cases were classified according to six classifications methods, (see Table 1).

Method 1

According Huang's method, we classified IBTR as either a TR or NP on the basis of tumour location and histology type [11]. An IBTR was designated as TR if it was located within the boost area or at the edge of that area and if the histology type was the same as that of the primary tumour. If the IBTR was located elsewhere in the breast or had a change in histology, it was designated as NP. In our cohort, this resulted in 118 TR, 115 NP, and just one of unknown classification.

Table 1 The six classification methods and their corresponding inclusion criteria

Inclusion criteria	Huang method	Yi method	Panet-Raymond method	Komoike method	Twente method	Morphology method
Localization IBTR	**X**	**X**	**X**	**X**	**X**	
Histology type	**X**	**X**	**X**	**X**	**X**	**X**
Oestrogen receptor		**X**	**X**		**X**	**X**
Human epidermal growth factor		**X**			**X**	**X**
Malignancy grading			**X**		**X**	**X**
Resection margin				**X**		

Table 2 Comparison of clinical, pathological, and treatment characteristics between 234 patients with an ipsilateral breast tumour recurrence (IBTR) as first event with true recurrence (TR) and new primary (NP) for two classification methods

Characteristics	Method 1 (Huang) $n=234$ (1 unknown)			Method 2 (Yi) $n=234$ (5 unknown)		
	TR $n=118$ (%)	NP $n=115$ (%)	p-value	TR $n=93$ (%)	NP $n=136$ (%)	p-value
Primary characteristics						
Age at primary diagnosis						
≤ 40 years	16 (13.6)	14 (12.2)		10 (10.7)	18 (13.2)	
41 = 50 years	33 (28.0)	34 (29.6)	0.933	26 (28.0)	40 (29.4)	0.793
> 50 years	69 (58.5)	67 (58.3)		57 (61.3)	78 (57.3)	
Median age	54	54		54	54	
Time to IBTR, mean (months)	121.3	155.9	**0.013**	123.5	1469.2	**0.020**
Histology primary						
Ductal carcinoma	99 (83.9)	73 (63.5)		77 (82.6)	91 (66.9)	
Lobular carcinoma	17 (14.4)	18 (15.6)		15 (16.3)	20 (14.7)	
Medullar carcinoma	0	7 (6.1)	**< 0.001**	0	7 (5.1)	**0.002**
Tubular carcinoma	1 (0.8)	12 (10.4)		1 (1.1)	12 (8.8)	
Rest	1 (0.8)	5 (4.3)		0	6 (4.4)	
Malignancy grading primary						
Grade 1	24 (20.3)	37 (32.2)		21 (22.8)	40 (29.4)	
Grade 2	51 (43.2)	43 (37.4)	0.183	43 (45.6)	51 (37.5)	0.272
Grade 3	32 (27.1)	31 (27.0)		22 (23.9)	40 (29.4)	
Unknown	11 (9.3)	4 (3.5)		7 (7.6)	5 (3.7)	
Lymph vascular space invasion primary						
Positive	18 (15.2)	11 (9.6)		14 (15.2)	15 (11.0)	
Negative	100 (84.8)	104 (90.4)	0.215	79 (84.8)	121 (89.0)	0.368
Mitotic Activity Index primary						
Low (< 13 in 2 mm^2)	82 (69.5)	72 (62.6)		69 (73.9)	84 (61.8)	
High (> 12 in 2 mm^2)	22 (18.6)	30 (26.1)	0.173	13 (14.1)	38 (27.9)	**0.013**
Unknown	14 (11.9)	13 (11.3)		11 (12.0)	14 (10.3)	
Oestrogen receptor status primary						
Positive	100 (84.7)	84 (73.0)		86 (92.4)	96 (70.6)	
Negative	16 (13.6)	28 (24.3)	**0.032**	5 (5.4)	37 (27.2)	**< 0.001**
Unknown	2 (2.6)	3 (2.6)		2 (2.2)	3 (2.2)	
Her2neu primary						
Negative	67 (56.8)	75 (65.2)		54 (57.6)	88 (65.7)	
Positive	4 (3.4)	7 (6.1)	0.488	3 (3.3)	8 (65.9	0.477
Unknown	47 (39.8)	33 (28.7)		36 (39.1)	40 (29.4)	
Margin status for invasive carcinoma						
Negative	93 (78.8)	102 (88.7)		72 (78.3)	119 (87.5)	
Positive	18 (15.2)	11 (9.6)	0.089	15 (15.2)	14 (10.3)	0.096
Marginal	7 (5.9)	2 (1.7)		6 (6.5)	3 (2.2)	
Adjuvant systemic therapy						
None	88 (74.6)	82 (71.3)		72 (77.2)	95 (69.8)	
Hormone therapy	14 (11.9)	15 (13.0)	0.862	10 (10.9)	19 (14.0)	0.303
Chemotherapy	8 (6.8)	11 (9.6)		4 (4.3)	14 (10.3)	
Hormone + chemotherapy	8 (6.8)	7 (6.1)		7 (7.6)	8 (5.9)	
Radiotherapy						
Breast only	98 (83.1)	95 (82.6)		77 (82.6)	112 (82.3)	
Breast + regional	20 (16.9)	20 (17.4)	0.929	16 (17.4)	24 (17.6)	0.900

Table 2 (continued)

Characteristics	Method 1 (Huang) $n=234$ (1 unknown)			Method 2 (Yi) $n=234$ (5 unknown)		
	TR $n=118$ (%)	NP $n=115$ (%)	p-value	TR $n=93$ (%)	NP $n=136$ (%)	p-value
IBTR characteristics						
Age at time IBTR						
≤ 50 years	16 (13.6)	13 (11.3)		10 (10.9)	17 (12.5)	
51–60 years	23 (19.5)	22 (19.1)	0.457	17 (18.5)	27 (19.8)	0.944
61–70 years	37 (31.4)	28 (24.3)		28 (29.3)	37 (27.1)	
> 70 years	42 (35.6)	52 (45.2)		38 (41.3)	55 (40.4)	
Median age	66	70		67	67	
Follow-up after IBTR, mean (months)	96.6	76.1	**0.023**	92.2	81.7	0.257
Histology of IBTR						
Ductal carcinoma	98 (83.0)	70 (60.9)		77 (82.6)	88 (64.7)	
Lobular carcinoma	17 (14.4)	26 (22.6)		15 (16.3)	28 (20.6)	
Tubular carcinoma	1 (0.8)	0	**< 0.001**	1 (1.1)	0	**0.001**
Rest	2 (1.7)	8 (7.0)		0	9 (6.6)	
Angiosarcoma	0	11 (9.6)		0	11 (8.1)	
Malignancy grading of IBTR						
Grade 1	19 (16.1)	25 (21.7)		15 (16.3)	28 (20.6)	
Grade 2	66 (55.1)	47 (40.9)	0.198	57 (60.9)	56 (41.2)	0.092
Grade 3	29 (24.6)	29 (25.2)		21 (22.8)	37 (27.2)	
Unknown	4 (4.2)	14 (12.2)		0	15 (11.0)	
Lymph vascular space invasion of IBTR						
Positive	17 (14.4)	16 (13.9)		16 (17.4)	17 (12.5)	
Negative	76 (64.4)	68 (59.1)	0.869	59 (64.1)	84 (61.8)	0.449
Unknown	25 (21.2)	31 (27.0)		18 (18.5)	35 (25.7)	
Mitotic Activity Index of IBTR						
Low (< 13 2 mm^2)	80 (67.8)	75 (65.2)		66 (71.7)	88 (64.7)	
High (> 12 2 mm^2)	23 (19.5)	19 (16.5)	0.717	16 (17.4)	26 (19.1)	0.579
Unknown	15 (12.7)	21 (18.3)		11 (10.9)	22 (16.2)	
Oestrogen receptor status of IBTR						
Positive	100 (84.7)	85 (73.9)		87 (94.6)	97 (71.3)	
Negative	15 (11.9)	16 (13.9)	0.558	6 (5.4)	25 (18.4)	**0.004**
Unknown	3 (3.4)	14 (12.2)		0	14 (10.3)	
Her2neu of IBTR						
Negative	92 (78.0)	89 (77.4)		82 (89.1)	98 (72.1)	
Positive	17 (14.4)	9 (7.8)	0.165	6 (6.5)	20 (14.7)	**0.030**
Unknown	9 (7.6)	17 (14.8)		5 (4.3)	18 (13.2)	
Ablation breast						
Yes	114 (96.6)	109 (94.8)		90 (96.7)	130 (95.6)	
None	2 (1.7)	5 (4.3)	0.240	1 (1.1)	5 (3.7)	0.232
Unknown	2 (1.7)	1 (0.9)		2 (2.2)	1 (0.7)	
Adjuvant therapy after IBTR						
None	43 (36.4)	51 (44.6)		31 (32.6)	61 (44.8)	
Yes	69 (58.5)	63 (54.5)	0.333	57 (62.0)	74 (54.4)	0.140
Unknown	6 (5.1)	1 (0.9)		5 (5.4)	1 (0.7)	

p-value has been calculated on the known components of the variables. Significant values are in bold

Table 3 Comparison of clinical, pathological, and treatment characteristics between 234 patients with an ipsilateral breast tumour recurrence (IBTR) as first event with true recurrence (TR) and new primary (NP) for two classification methods

Characteristics	Method 3 (Panet-Raymond) $n=234$ (2 unknown)			Method 4 (Komoike) $n=234$ (3 unknown)		
	TR $n=100$ (%)	NP $n=132$ (%)	p-value	TR $n=121$ (%)	NP $n=110$ (%)	p-value
Primary characteristics						
Age at primary diagnosis						
≤ 40 years	13 (13.0)	17 (12.9)		16 (13.2)	14 (12.7)	
41–50 years	28 (28.0)	39 (29.5)	0.967	33 (27.3)	32 (29.1)	0.959
> 50 years	59 (59.0)	76 (57.6)		72 (59.5)	64 (58.2)	
Median age	53.5	54		54	53.5	
Time to IBTR, mean (months)	120.1	152.3	**0.003**	120.4	156.2	**0.001**
Histology primary						
Ductal carcinoma	82 (82.0)	89 (67.4)		100 (82.6)	70 (63.6)	
Lobular carcinoma	15 (15.0)	20 (15.1)		17 (14.1)	18 (16.4)	
Medullar carcinoma	0	7 (5.3)	**0.013**	0	7 (6.4)	**0.001**
Tubular carcinoma	2 (2.0)	11 (8.3)		2 (1.6)	11 (10.0)	
Rest	1 (1.0)	5 (3.8)		2 (1.6)	4 (3.6)	
Malignancy grading primary						
Grade 1	21 (21.0)	40 (30.3)		25 (20.7)	34 (30.9)	
Grade 2	44 (44.0)	50 (37.8)	0.296	52 (43.0)	42 (38.2)	0.286
Grade 3	25 (25.0)	38 (28.8)		33 (27.3)	30 (27.2)	
Unknown	10 (10.0)	4 (3.0)		11 (9.1)	4 (3.6)	
Lymph vascular space invasion primary						
Positive	16 (16.0)	13 (9.8)		19(15.7)	10 (9.1)	
Negative	84 (84.0)	119 (90.1)	0.161	102 (84.3)	100 (90.9)	0.130
Mitotic Activity Index primary						
Low (< 13 in 2 mm^2)	70 (70.0)	84 (63.6)		83 (68.6)	69 (62.7)	
High (> 12 in 2 mm^2)	16 (16.0)	36 (27.3)	0.063	23 (19.0)	29 (26.4)	0.196
Unknown	14 (14.0)	12 (9.1)		15 (12.4)	12 (10.9)	
Oestrogen receptor status primary						
Positive	90 (90.0)	93 (70.4)		102 (84.3)	80 (72.7)	
Negative	9 (9.0)	35 (26.5)	**0.001**	16 (14.1)	27 (24.5)	**0.038**
Unknown	1 (1.0)	4 (3.1)		3 (2.7)	3 (2.7)	
Her2neu primary						
Negative	58 (58.0)	84 (63.6)		70 (57.8)	72 (65.4)	
Positive	4 (4.0)	7 (5.3)	0.771	4 (3.3)	7 (6.4)	0.408
Unknown	38 (38.0)	41 (31.1)		47 (38.8)	31 (28.2)	
Margin status for invasive carcinoma						
Negative	78 (78.0)	116 (87.9)		94 (77.7)	99 (90.0)	
Positive	15 (15.0)	14 (10.6)	0.051	20 (16.5)	9 (8.2)	**0.037**
Marginal	7 (7.0)	2 (1.5)		7 (5.8)	2 (1.8)	
Adjuvant systemic therapy						
None	77 (77.0)	92 (69.7)		90 (74.4)	78 (70.9)	
Hormone therapy	10 (10.0)	19 (14.4)	0.493	15 (12.4)	14 (12.7)	0.823
Chemotherapy	6 (6.0)	13 (9.8)		8 (6.6)	11 (10.0)	
Hormone + chemotherapy	7 (7.0)	8 (6.1)		8 (6.6)	7 (6.4)	
Radiotherapy						
Breast only	83 (83.0)	109 (82.6)		102 (84.3)	90 (81.8)	
Breast + regional	17 (17.0)	23 (17.4)	0.932	19 (15.7)	20 (18.2)	0.615

Table 3 (continued)

Characteristics	Method 3 (Panet-Raymond) $n=234$ (2 unknown)			Method 4 (Komoike) $n=234$ (3 unknown)		
	TR $n=100$ (%)	NP $n=132$ (%)	p-value	TR $n=121$ (%)	NP $n=110$ (%)	p-value
IBTR characteristics						
Age at time IBTR						
≤ 50 years	15 (15.0)	14 (10.6)		16 (13.2)	13 (11.8)	
51–60 years	18 (18.0)	27 (20.4)	0.504	24 (19.8)	21 (19.1)	0.695
61–70 years	31 (31.0)	34 (25.8)		36 (29.7)	27 (24.5)	
> 70 years	36 (36.0)	57 (43.2)		45 (37.2)	49 (44.5)	
Median age	65.5	69		66	70	
Follow-up after IBTR, mean (months)	98.3	78.0	**0.026**	97.4	74.4	**0.011**
Histology of IBTR						
Ductal carcinoma	83 (83.0)	85 (64.4)		98 (81.0)	68 (61.8)	
Lobular carcinoma	15 (15.0)	28 (21.2)		19 (15.7)	24 (21.8)	
Tubular carcinoma	1 (1.0)	0	**0.002**	1 (0.8)	0	**0.001**
Rest	1 (1.0)	8 (6.1)		3 (2.5)	7 (6.4)	
Angiosarcoma	0	11 (8.3)		0	11 (10.0)	
Malignancy grading of IBTR						
Grade 1	17 (17.0)	27 (20.4)		21 (17.4)	23 (20.9)	
Grade 2	60 (59.0)	53 (40.1)	**0.043**	68 (56.2)	44 (40.0)	0.201
Grade 3	20 (20.0)	38 (28.8)		28 (23.1)	29 (26.4)	
Unknown	3 (4.0)	14 (10.6)		4 (3.3)	14 (12.7)	
Lymph vascular space invasion of IBTR						
Positive	14 (14.0)	19 (14.4)		17 (14.1)	16 (14.5)	
Negative	64 (64.0)	80 (60.6)	0.833	78 (64.5)	65 (59.1)	0.753
Unknown	22 (22.0)	33 (25.0)		26 (21.5)	29 (26.4)	
Mitotic Activity Index of IBTR						
Low (< 13 2 mm^2)	71 (71.0)	84 (63.6)		82 (67.8)	72 (65.4)	
High (> 12 2 mm^2)	16 (16.0)	26 (19.7)	0.372	23 (19.0)	19 (17.3)	0.861
Unknown	13 (13.0)	22 (16.7)		16 (13.2)	19 (17.3)	
Oestrogen receptor status of IBTR						
Positive	91 (91.0)	94 (71.2)		103 (85.1)	80 (72.7)	
Negative	7 (6.0)	24 (18.2)	**0.006**	15 (12.4)	16 (14.5)	0.414
Unknown	2 (3.0)	14 (10.6)		3 (2.5)	14 (12.7)	
Her2neu of IBTR						
Negative	80 (80.0)	101 (76.5)		95 (78.5)	84 (76.4)	
Positive	12 (12.0)	14 (10.6)	0.851	17 (14.0)	9 (8.2)	0.239
Unknown	8 (8.0)	17 (12.9)		9 (7.4)	17 (15.4)	
Ablation breast						
Yes	98 (98.0)	125 (94.7)		117 (96.7)	104 (94.5)	
None	1 (1.0)	5 (3.8)	0.183	2 (1.6)	5 (4.5)	0.204
Unknown	1 (1.0)	2 (1.5)		2 (1.6)	1 (0.9)	
Adjuvant therapy after IBTR						
None	33 (33.0)	60 (45.4)		42 (34.7)	50 (45.4)	
Yes	62 (62.0)	70 (53.0)	0.086	73 (60.3)	59 (53.6)	0.155
Unknown	5 (5.0)	2 (1.6)		6 (5.0)	1 (0.9)	

p-value has been calculated on the known components of the variables. Significant values are in bold

Table 4 Comparison of clinical, pathological, and treatment characteristics between 234 patients with an ipsilateral breast tumour recurrence (IBTR) as first event with true recurrence (TR) and new primary (NP) for two classification methods

Characteristics	Method 5 (Twente) $n=234$ (6 unknown)			Method 6 (Morphology) $n=234$ (14 unknown)		
	TR $n=90$ (%)	NP $n=138$ (%)	p-value	TR $n=114$ (%)	NP $n=106$ (%)	p-value
Primary characteristics						
Age at primary diagnosis						
≤ 40 years	10 (11.1)	19 (13.8)		13 (11.5)	16 (15.1)	
41 = 50 years	26 (28.9)	40 (29.0)	0.830	27 (23.9)	36 (34.0)	0.109
> 50 years	54 (60.0)	79 (57.2)		74 (64.6)	54 (50.9)	
Median age	54	53.5		55.5	51	
Time to IBTR, mean (months)	122.3	149.9	**0.014**	117.0	154.6	**0.000**
Histology primary						
Ductal carcinoma	74 (82.2)	94 (68.1)		93 (81.4)	66 (62.3)	
Lobular carcinoma	15 (16.7)	20 (14.5)		19 (16.8)	16 (15.1)	
Medullar carcinoma	0	7 (5.1)	**0.005**	0	7 (6.6)	**< 0.001**
Tubular carcinoma	1 (1.1)	12 (8.7)		1 (0.9)	12 (11.3)	
Rest	0	5 (3.6)		1 (0.9)	5 (4.7)	
Malignancy grading primary						
Grade 1	19 (21.1)	42 (30.4)		25 (22.1)	35 (33.0)	
Grade 2	43 (47.8)	51 (37.0)	0.148	58 (50.4)	35 (33.0)	**0.029**
Grade 3	22 (24.4)	41 (29.7)		30 (26.5)	33 (31.3)	
Unknown	6 (6.7)	4 (2.9)		1 (0.9)	3 (2.8)	
Lymph vascular space invasion primary						
Positive	14 (15.7)	15 (10.9)		13 (11.5)	14 (13.2)	
Negative	76 (84.3)	123 (89.1)	0.299	101 (88.5)	92 (86.8)	0.684
Mitotic Activity Index primary						
Low (< 13 in 2 mm^2)	67 (74.4)	86 (62.3)		88 (77.0)	65 (61.3)	
High (> 12 in 2 mm^2)	13 (14.4)	39 (28.3)	**0.016**	19 (16.8)	32 (30.2)	**0.012**
Unknown	10 (11.1)	13 (9.4)		7 (6.2)	9 (8.5)	
Oestrogen receptor status primary						
Positive	84 (94.4)	97 (70.3)		98 (86.7)	75 (70.7)	
Negative	5 (4.5)	37 (26.8)	**< 0.001**	16 (13.3)	27 (25.5)	**0.022**
Unknown	1 (1.1)	4 (2.9)		0	4 (3.8)	
Her2neu primary						
Negative	53 (58.4)	89 (64.5)		74 (64.6)	68 (64.1)	
Positive	3 (3.4)	8 (5.8)	0.505	4 (3.5)	6 (5.7)	0.459
Unknown	34 (38.2)	41 (29.7)		36 (31.9)	32 (30.2)	
Margin status for invasive carcinoma						
Negative	69 (77.5)	122 (88.4)		88 (77.9)	95 (89.6)	
Positive	15 (15.7)	13 (9.4)	**0.050**	20 (16.8)	8 (7.5)	**0.047**
Marginal	6 (6.7)	3 (2.2)		6 (5.3)	3 (2.8)	
Adjuvant systemic therapy						
None	70 (77.5)	96 (69.6)		88 (77.0)	74 (69.8)	
Hormone therapy	9 (10.1)	19 (13.8)	0.245	10 (8.8)	15 (14.1)	0.443
Chemotherapy	4 (4.5)	15 (10.9)		8 (7.1)	11 (10.4)	
Hormone + chemotherapy	7 (7.9)	8 (5.8)		8 (7.1)	6 (5.7)	
Radiotherapy						
Breast only	75 (83.3)	115 (83.3)		95 (83.2)	90 (84.9)	
Breast + regional	15 (16.7)	23 (16.7)	1.000	19 (16.8)	16 (15.1)	0.750

Table 4 (continued)

Characteristics	Method 5 (Twente) $n=234$ (6 unknown)			Method 6 (Morphology) $n=234$ (14 unknown)		
	TR $n=90$ (%)	NP $n=138$ (%)	p-value	TR $n=114$ (%)	NP $n=106$ (%)	p-value
IBTR characteristics						
Age at time IBTR						
≤ 50 years	10 (11.2)	17 (12.3)		15 (13.3)	12 (11.3)	
51–60 years	17 (19.1)	28 (20.3)	0.956	20 (17.7)	24 (22.6)	0.751
61–70 years	27 (29.2)	37 (26.8)		36 (31.0)	29 (27.4)	
> 70 years	36 (40.4)	56 (40.6)		43 (38.0)	41 (38.7)	
Median age	66	67.5		66	67	
Follow-up after IBTR, mean (months)	93.4	80.4	0.163	91.4	80.1	0.225
Histology of IBTR						
Ductal carcinoma	74 (82.0)	91 (65.9)		92 (80.5)	64 (60.4)	
Lobular carcinoma	15 (16.8)	28 (20.3)		20 (17.7)	23 (21.7)	
Tubular carcinoma	1 (1.1)	0	**0.003**	1 (0.9)	0	**< 0.001**
Rest	0	8 (5.8)		1 (0.9)	8 (7.5)	
Angiosarcoma	0	11 (8.0)		0	11 (10.4)	
Malignancy grading of IBTR						
Grade 1	15 (16.8)	29 (21.0)		23 (20.3)	19 (17.9)	
Grade 2	57 (62.9)	55 (39.9)	**0.022**	61 (53.1)	46 (43.4)	0.689
Grade 3	18 (20.2)	40 (29.0)		29 (25.7)	29 (27.4)	
Unknown	0	14 (10.1)		1 (0.9)	12 (11.3)	
Lymph vascular space invasion of IBTR						
Positive	16 (18.0)	17 (12.3)		19 (16.8)	12 (11.3)	
Negative	56 (62.9)	87 (63.0)	0.326	73 (64.6)	65 (61.3)	0.397
Unknown	18 (19.1)	34 (24.6)		22 (18.6)	29 (27.4)	
Mitotic Activity Index						
Low (< 13 in 2 mm^2)	65 (73.0)	89 (64.5)		78 (69.0)	70 (66.0)	
High (> 12 in 2 mm^2)	15 (16.8)	27 (19.6)	0.448	23 (20.3)	17 (16.0)	0.589
Unknown	10 (10.1)	22 (15.9)		13 (10.6)	19 (17.9)	
Oestrogen receptor status of IBTR						
Positive	85 (95.5)	98 (71.0)		100 (88.5)	75 (70.7)	
Negative	5 (4.5)	26 (18.8)	**0.002**	14 (11.5)	17 (16.0)	0.216
Unknown	0	14 (10.2)		0	14 (13.2)	
Her2neu of IBTR						
Negative	78 (87.6)	102 (73.9)		103 (91.1)	72 (67.9)	
Positive	7 (7.9)	19 (13.8)	0.112	7 (6.2)	18 (17.0)	**0.004**
Unknown	5 (4.5)	17 (12.3)		4 (2.6)	16 (15.1)	
Ablation breast						
Yes	87 (96.6)	132 (95.6)		111 (97.4)	101 (95.3)	
None	1 (1.1)	5 (3.6)	0.253	1 (0.9)	4 (3.8)	0.152
Unknown	2 (2.2)	1 (0.7)		2 (1.7)	1 (0.9)	
Adjuvant therapy after IBTR						
None	29 (31.5)	62 (44.9)		38 (32.7)	51 (48.1)	
Yes	56 (62.9)	75 (54.3)	0.101	71 (62.8)	54 (50.9)	**0.042**
Unknown	5 (5.6)	1 (0.7)		5 (4.4)	1 (1.0)	

p-value has been calculated on the known components of the variables. Significant values are in bold

Method 2

According to Yi's methods, we classified IBTR as either a TR or NP on the basis of tumour location and histology type, oestrogen receptor status, and human epidermal growth factor receptor 2 (HER2) status [13]. IBTR was designated as TR if all of the following applied: (1) it was located within the boost area or at the edge of this area; (2) the histology type was consistent with the primary tumour; (3) both oestrogen receptor; and (4) HER2 status were consistent with the primary tumour. If the IBTR failed to meet any of these four criteria, it was designated as NP. At least three had to be known for classifying the IBTR as TR or NP. This resulted in 93 TR, 136 NP, and 5 unknowns.

Method 3

Panet-Raymond et al. used a classification based on pathological and location information [12]. They designed a decision rule algorithm, classifying patients based on change in histology, histological grade, oestrogen receptor status, and tumour location. Only a change from grade III to grade I was considered to be significant. This resulted in 100 TR, 132 NP, and two unknowns.

Method 4

Komoike et al. classified IBTR, based on tumour location, initial surgical margin, and pathological findings, as histological subtype [14]. If the IBTR was located at the primary site or close, it was TR. In cases with tumour-positive resection margins, especially with tumours located narrowly apart, primary and IBTR, it was defined as a TR. Cases with negative or positive margins and located elsewhere were defined as a NP. Those located at the primary site or close with negative margins and IBTR histologically different from primary tumour were defined as a NP. This resulted in 121 TR, 110 NP, and just three unknowns.

Method 5

For our Twente method, we used a combination of methods one, two, and three. IBTR was designated as TR if it (1) was located within the boost area or at the edge of this area; (2) if the histology type was consistent with the primary tumour; and (3) if malignancy grading; (4) oestrogen receptor status; and (5) HER2 status were all consistent with the primary tumour. Only a change from grade III to grade I was considered to be significant. If the IBTR failed to meet any of these criteria, it was designated as NP. Due to the long timeframe of this study, not all five items were always known. At least four items had to be known for classifying the IBTR as TR or NP. This resulted in 90 TR, 138 NP, and 6 unknowns.

Method 6

For our Morphology method, we used only the morphological criteria used in the above-mentioned methods: (1) histological type; (2) malignancy grading; (3) oestrogen receptor; and (4) HER2 status. All the criteria have to be concordant between the primary tumour and IBTR to be considered a TR. Only a change from grade III to grade I was considered significant. Since not all criteria were known due to the long timeframe of the study, at least three of the four criteria had to be known. This resulted in 114 TR, 106 NP, and 14 unknowns.

Statistical methods

Time to recurrence and length of follow-up were calculated from the date of the lumpectomy. To test between-group differences in categorical data, Chi-square tests were used, and these analyses with regard to local recurrences were performed in relation to the number of BCTs. Statistics for distant metastases were calculated by applying the Kaplan and Meier method. For all survival analyses, patients were censored if they had not experienced an event (IBTR, regional recurrence, distant metastases) at the date of the most recent follow-up or at the date of death.

The Cox proportional hazards model was used to test the independent effect of IBTR after adjusting for known prognostic factors and hazard ratios (HR) estimated with 95% confidence limits.

For comparison of recurrence distributions, the log-rank test was used. For comparison of longitudinal variables the Wilcoxon rank-sum test was used. Variables that were univariate related to the outcomes of interest ($p < 0.05$) were input into multivariate analyses.

Analyses were performed using STATA 14.2 (Stata Corp, College Station, TX).

The Twente Medical Ethical Committee approved the analysis on the data.

Results

The clinical, pathological, and treatment characteristics of all IBTRs and diagnosed as first event for the various methods are shown in Tables 2, 3 and 4.

Based on these characteristics, all six methods revealed (a) a longer time interval till diagnosis of the IBTR for NP compared to TR; (b) more ductal carcinoma for TR compared to NP; (c) more primary oestrogen-negative status for NP compared to TR; (d) a longer follow-up after diagnosis

of the IBTR for TR; and (e) all angiosarcomas within the pathology of the IBTR were recorded as NP.

Disease-specific survival after IBTR

The follow-up after IBTR ranged from 2 to 392 months with a median of 71 months.

The 10-year DSS for the whole cohort of 234 IBTR was 69.4%.

For the classification methods 1 to 6, the 10-year DSS values for TR and NP were (1) 67.3% and 72.5%; (2) 64.0% and 74.8%; (3) 66.5% and 72.4%; (4) 68.2% and 71.0%; (5) 62.8% and 75.2%; and (6) 65.3% and 75.3%, respectively. None of the six methods showed significant differences in DSS between TR and NP in univariate analyses.

Figure 1 shows the DSS figures of the various methods for TR and NP.

In a 10-year DSS Cox regression multivariate analysis, taking into account those variables that were found to be significant in univariate analyses, the HR for NP compared to TR for the methods 1 to 6 were (1) HR 1.1 (95% CI 0.6–2.1); (2) HR 0.6 (95% CI 0.3–1.1); (3) HR 1.0 (95% CI 0.5–1.9); (4) HR 1.2 (95% CI 0.6–2.2); (5) HR 0.5 (95% CI 0.2–1.0); and (6) HR 0.5 (95% CI 0.3–1.1), respectively. Figure 2 shows the HR with confidence intervals for NP compared to TR for the various classification methods.

Distant metastasis-free survival after IBTR

In a 10-year DMFS Cox regression multivariate analysis, taking into account the significant variables from our univariate analyses the HR for NP compared to TR for the methods 1 to 6 were (1) HR 0.9 (95% CI 0.5–1.6); (2) HR 0.7 (95% CI 0.4–1.3); (3) HR 0.8 (95% CI 0.4–1.4); (4) HR 0.9 (95% 0.5–1.6); (5) HR 0.6 (95% CI 0.4–1.2); and (6) HR 0.6 (95% CI 0.3–1.1), respectively. Figure 3 shows the HR with confidence intervals for NP compared to TR for the various classification methods.

Sensitivity analysis

Due to the long timeframe of this study some variables (Tables 2, 3, and 4), particularly the HER2 of the primary tumour were not available which can have a main impact on the TR. Therefore, we performed our classification for methods 2, 5, and 6, where at least three criteria, four, and three, respectively, had to be known for primary as well as for the IBTR. To investigate the impact of missing variables, we performed a sensitivity explorative analysis for methods 2, 5, and 6 when all known criteria were present. For method 2 this resulted in 56 TR, 136 NP, and 42 unknown, for method 5 in 55 TR, 138 NP, and 41 unknown, and for method 6 in 77 TR, 106 NP, and 51 unknown.

The outcomes of the HR for NP compared to TR of the multivariate 10-year DSS were for method 2 a HR of 0.6 (95% CI 0.3–1.2), for method 5 a HR of 0.6 (95% CI 0.3–1.2), and for method 6 a HR of 0.6 (95% CI 0.3–1.4), respectively.

The outcome of the HR for NP compared to TR of the multivariate 10-year DMFS were for method 2 a HR of 0.7 (95% CI 0.3–1.2), for method 5 a HR of 0.6 (95% CI 0.3–1.2), and for method 6 a HR of 0.6 (95% CI 0.3–1.2), respectively.

Discussion

This study has demonstrated that DSS and DMFS depend upon the classification method used for TR and NP.

In this study, we compared six methods for classifying a first event IBTR as TR or NP.

Currently, when an IBTR is diagnosed after BCT, it is common practice to associate IBTR with a good or poor prognosis that might have direct implications for the use of (neo)adjuvant systemic therapy. Various methods have been discussed in the literature to consider those implications; for instance, the timing of the IBTR after primary treatment. The occurrence of early IBTR, when compared to a late IBTR, may be associated with a worse outcome [8, 9]. Another way of looking at IBTRs is to classifying these events into true local recurrences (TR) and new primaries (NP) [10–14]. The hypothesis was that early IBTR and late IBTR may correspond to two distinct types of IBTR: (a) TR, corresponding to regrowth of resistant cells after initial treatment and (b) NP, corresponding to new cancer growth. In the literature, many classifications of TR and NP are used, but no generally accepted classification yet exists.

We compared the two classification methods used by the M. D. Anderson Cancer Centre, one used by the British Colombia Cancer Agency, and the one used by the Osaka Medical Centre for Cancer [10–13]. In an attempt to optimize classification, we created two other classification methods: (a) the Twente method (method 4), based on the first three methods, combining all selection criteria used and (b) the Morphological method (method 6) using only the morphological criteria and leaving out the clinical ones.

The latter method was chosen, because with multi-focal and multi-centric primary tumours, there can be a TR, of the same morphological tumour, not within or near the primary area of the primary, but elsewhere in the breast.

For this study we selected all IBTRs as first event in patients with unilateral breast cancer. This was to achieve a homogeneous selection of IBTR without any interaction

from contra-lateral breast cancer, as demonstrated in our earlier studies [15, 16].

Comparing the clinical, pathological, and treatment characteristics of the IBTR, as first event, in relation to TR versus NP, we noted that they were comparable for all six methods. Except for the oestrogen receptor of the IBTR, methods 2, 3, and 5 showed significant differences between TR and NP. Also, for the HER2 of the IBTR we noted differences between method 2 and 6. All six methods showed an earlier occurrence of TR versus NP, comparable with outcomes described in the literature [10–14]. The significant difference demonstrated between TR and NP for the histological subtype of the IBTR was, in all methods, mainly the result of the difference in the occurrence of ductal carcinoma between TR and NP. The presence of angiosarcomas in NP also contributed to this difference.

For DSS, we found for three methods (numbers 2, 5, and 6) a better DSS for NP compared to TR. The other three showed no or only marginally better DSS for NP. Looking at the HR and confidence intervals (CI) of the first three

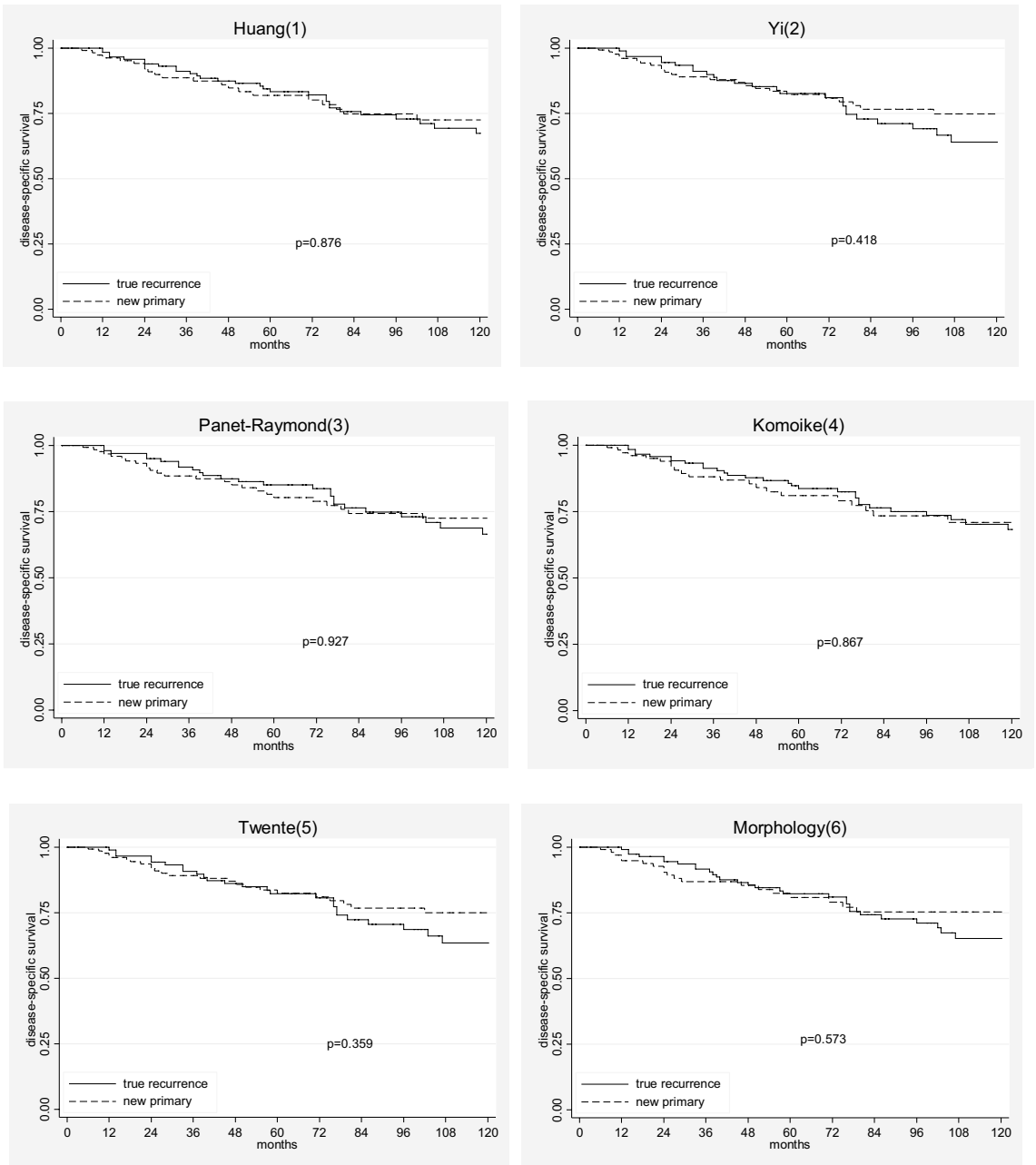

Fig. 1 The 10-year disease-specific survival (DSS) of 234 women with IBTR as first event from the time of the IBTR, according to true recurrence and new primary for the six different classification methods. The unknowns are excluded from the figures

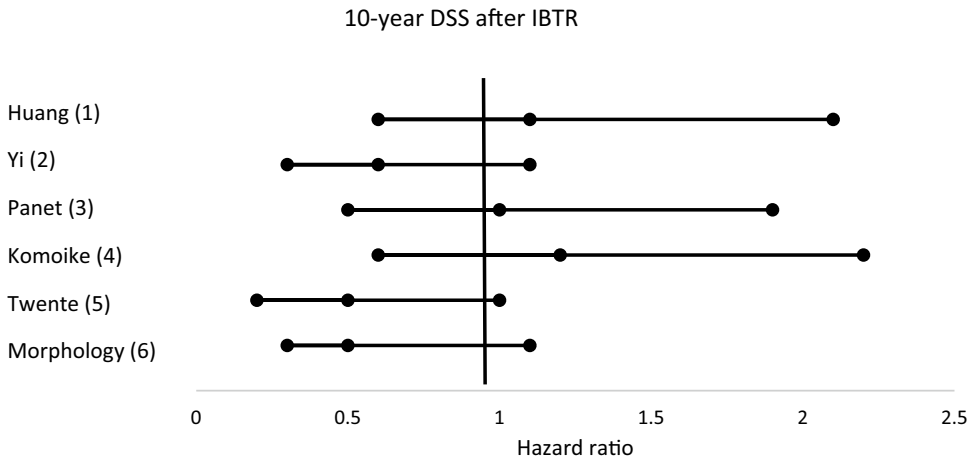

Fig. 2 The hazard ratios with the 95% confidence intervals of the 10-year disease-specific survival (DSS) after the diagnosis of the IBTR of 234 ipsilateral breast tumour recurrences (IBTR) as first event for the new primaries compared to true recurrences

methods, the Twente method and the Morphology methods result in a lower HR compared to the Yi method, although the confidence intervals are comparable.

With respect to DMFS, we found that for all methods a better NP compared to TR with a HR ranging from 0.6 to 0.9, with the lowest HR for the Twente method and the Morphology method. Taking into account the CIs, we noted the narrowest CI for the Twente method and the Morphology method.

For DSS and DMFS, the Twente method and the Morphology method seemed the most powerful methods of differentiating prognosis between NP and TR. However, we have to take into account that the numbers of IBTRs are small, so this has to be interpreted with caution. However, the absolute numbers of IBTRs in this study were within the range (126–397) used in the methods reported by Huang, Yi, Panet-Raymond, and Komoike.

Taking into account sometimes the small differences in HRs between the various methods leads to the question of whether we are dealing with the most suitable criteria for classifying NP and TR.

Considering the criteria used for the various methods, histological subtype was used by all and also the location of the IBTR except for the Morphology method. In Huang's method, these were the only two criteria used, whilst Panet-Raymond added malignancy grade and oestrogen status, and Yi added both HER2 status and oestrogen status. For the Yi method, this resulted in a better DSS and DMFS for NP. For the Panet-Raymond method, we noted a better DMFS and no better DSS for NP. We noted in the Twente method with all criteria used by Huang, Yi, and Panet-Raymond, a better discrimination between TR and NP. We did not incorporate the surgical margin, because surgical margin and location of the IBTR in relation to the primary location are two non-morphological criteria, which may contradict each other, so that a choice has to be made between the two. Also, surgical margin in combination with other criteria depends on the oncologist's interpretation, as noted by Komoike.

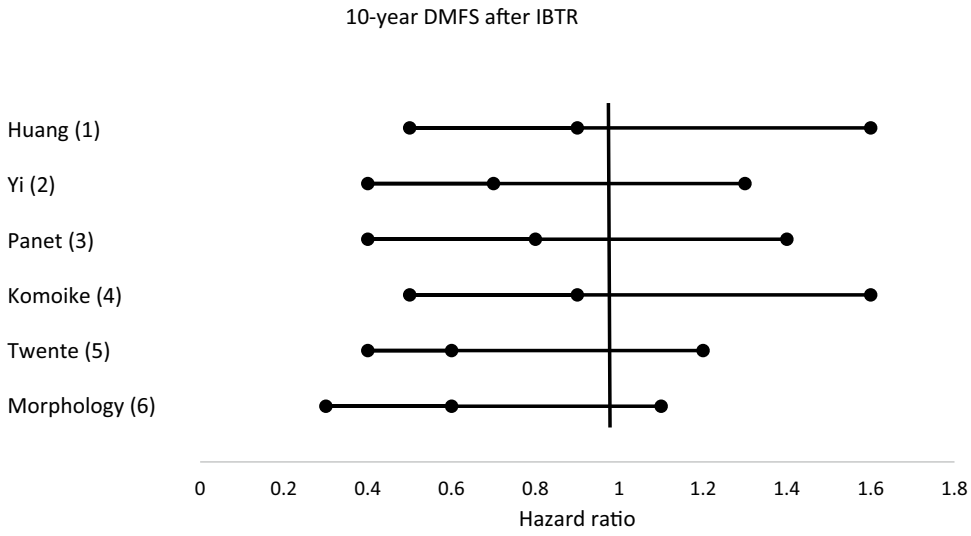

Fig. 3 The hazard ratios with the 95% confidence intervals of the 10-year distant metastases-free survival (DMFS) after the diagnosis of the IBTR of 234 ipsilateral breast tumour recurrences (IBTR) as first event for the new primaries compared to true recurrences

In the Morphological method, we excluded the clinical criteria used in the other five methods and this led to good discrimination with respect to NP versus TR with HRs of 0.6 and 0.5, respectively. That outcome brings into doubt the relevance of location of the IBTR as a valid criterion.

Despite the positive result with respect to predicting outcomes for the Twente method and the Morphology method, this study also stresses the need for further research in classifying IBTRs into NP and TR.

Due to the timeframe of this study a number of variables were unknown, for instance, the HER2 status of the primary. We therefore limited the number of known criteria for method 2, 5, and 6. To look for possible differences in outcome between methods with a limited number of known criteria compared to where all criteria had to be known, we performed an explorative analysis for the latter. The results were extremely similar.

Another difference between this study and previous studies is the exclusion of patients with contra-lateral breast cancer [15, 16]. In our study, we excluded those patients to prevent any bias, due to the potential interaction between contra-lateral breast cancer and IBTR. Having contra-lateral breast cancer might lead to the use of adjuvant systemic therapy, which might have an additional effect on the prognosis of the IBTR. We also limited ourselves to patients with an invasive IBTR, since ductal carcinoma in situ as IBTR has a better prognosis.

The present study has some limitations. Due to the long timeframe of this study, not all data necessary for classification were available. However, our study also has several strengths, including the large overall sample size, a timeframe of about 30 years, a prospectively population-based design, a single-centre study with respect to the radiotherapy and pathology, high-quality clinical data, and nearly no loss of follow-up (0.4%).

In conclusion, this study has demonstrated that using additional criteria for classifying IBTR into TR and NP, as in the Twente method, has been shown to give a more reliable insight into the prognostic value of this form of classification. It also stresses the need for further testing, with less unknown inclusion criteria, of the hypothesis that TR and NP are two distinct entities.

Author contributions Conception and design: JJJ and HS, Data collection: JJJ, Analysis and interpretation: JJJ, HS, and JvdP, Writing of the manuscript: JJJ, HS, JvdP, ES, and HJH. Approval of final article: JJJ, HS, JvdP, ES, and HJH. All authors have read and approved the final manuscript.

Funding The authors declare that there have been no funding.

Data availability All data generated or analysed during this study are included in this published article.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were followed in accordance with the ethical standards of the institution.

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

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