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Consensus Statement

Multifocality in ipsilateral breast tumor recurrence - A study in ablative specimens

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ABSTRACT

Background: The incidence and clinical significance of multifocality in ipsilateral breast tumor recurrence (IBTR) after breast-conserving therapy (BCT) are unclear. With growing interest in repeat BCT, this information has become of importance. This study aimed to gain insight in the incidence of multifocality in IBTR, to identify patient- and tumor-related predicting factors and to investigate the prognostic significance of multifocality.

Methods: Two hundred and fifteen patients were included in this analysis. All had an IBTR after BCT and were treated by salvage mastectomy and appropriate adjuvant therapy. Predictive tumor- and patient-related factors for multifocality in IBTR were identified using X2 test and univariate logistic regression analyses. Prognostic outcomes were calculated using Kaplan Meier analysis and compared using the log rank test.

Results: Multifocality was present in 50 (22.9%) of IBTR mastectomy specimens. Axillary positivity in IBTR was significantly associated with multifocality in IBTR. Chest wall re-recurrences occurred more often after multifocal IBTR (14% versus 7% after unifocal IBTR, $p = 0.120$). Regional re-recurrences did not differ significantly between unifocal and multifocal IBTR (8% vs. 6%, $p = 0.773$). Distant metastasis after salvage surgery occurred more frequently after multifocal IBTR (15% vs. 24%, $p = 0.122$). Overall survival was 132 months after unifocal IBTR and 112 months after multifocal IBTR ($p = 0.197$).

Conclusion: The prevalence of multifocality in IBTR is higher than in primary breast cancer. Axillary positivity in IBTR was associated with a multifocal IBTR. Chest wall re-recurrences and distant metastasis were, although not statistically significant, more prevalent after multifocal IBTR.

Introduction

Multifocality in breast cancer is commonly defined as the presence of two or more separate tumor foci in the same breast. The incidence of multifocality reported in literature for primary breast cancer is approximately 10% [1]. Multifocal tumors are associated with a worse prognosis, both for local and distant recurrence and overall survival [1–8]. The definition of multifocality in literature varies greatly. Generally, the term multifocality is reserved for tumors with one or more additional foci of invasive or in situ carcinoma within the same quadrant, whereas multicentricity implies the presence of tumor in other quadrants of the breast [9]. The

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clinical impact of multifocality depends on the invasiveness of the additional foci. It appears that only invasive foci have a negative impact on prognosis, whereas the finding of additional DCIS lesions does not seem to be associated with a worse outcomes after lumpectomy followed by radiotherapy [10].

Whereas breast-conserving therapy (BCT) is widely accepted as the treatment of first choice for the majority of women with primary breast cancer, the finding of multifocality during preoperative workup is still frequently considered a reason to prefer mastectomy [11]. The surgical feasibility of BCT in case of multifocality is limited, especially in smaller breasts. Furthermore, oncologically, a mastectomy is hypothesized to allow for better local control by surgically removing potential other, occult on imaging, lesions in the breast. The increased use of more sensitive imaging techniques like breast magnetic resonance imaging (MRI) in the preoperative workup for patients eligible for breast-conserving therapy (BCT) has a substantial impact on surgical treatment [12]. To date, there is little evidence that mastectomy is more safe than BCT for multifocal tumors, when looking at the risk of locoregional and distant recurrences [13,14]. BCT appears to be a safe treatment option in small multifocal tumors in the same quadrant of the breast [15].

Even with a very good prognosis after modern multimodality treatment for breast cancer [16–18], patients treated with BCT remain at risk for ipsilateral breast tumor recurrence (IBTR), with yearly risks varying between 0.5 and 1% per year [19]. The surgical gold standard for the treatment of IBTR is salvage mastectomy, but there is growing evidence for the feasibility of a repeat BCT in selected cases [20–22]. Multifocal IBTR is generally considered a contraindication for repeat BCT [23–26].

The prevalence of multifocality in patients with IBTR after initial BCT is unclear. Assuming that multifocality is an expression of a more aggressive behavior of the tumor and that IBTR can also be interpreted as a sign of tumor aggressiveness, one would expect the prevalence of multifocality to be higher in IBTR than in primary breast cancer. The aim of this study is to determine the prevalence of multifocality in salvage mastectomy specimens for IBTR after initial BCT and to identify tumor- and patient-related factors that are associated with a higher risk of multifocality in IBTR. The current high mastectomy rate in the surgical treatment of IBTR allows for this accurate determination of the presence of additional foci and can help us establish whether a repeat BCT might be considered in a larger number of patients than is currently done.

Materials and methods

Patient selection and inclusion

For the present study, patients were selected from the Sentinel Node and Recurrent Breast Cancer (SNARB) study population [27]. A total of 515 patients with operable IBTR were registered in the SNARB database. For the present study, 266 patients from five large participating centers were screened for eligibility. Inclusion criteria were 1) primary breast cancer treated by BCT, 2) treatment by salvage mastectomy and 3) availability of histopathological information regarding the presence of multifocality.

Ablative specimens and definition of multifocality

Multifocality was defined as the presence of at least one additional invasive or in situ lesion in the ipsilateral breast, either in the same quadrant or elsewhere, separated by normal breast tissue. No distinction could be made between multifocal and multicentric tumors due to the retrospective nature of this study. All mastectomy specimens had been handled according to the current guidelines [28] and reviewed by experienced pathologists, which included sampling of the specimens in slices of maximum 10 mm and checking for margin involvement and additional lesions by specimen radiography. Estrogen receptor (ER) and progesterone receptor (PR) positivity were defined as staining of >10% of cell nuclei by immunohistochemistry. Her2Neu positivity was defined as 2+ (only when confirmed by fluorescent in-situ hybridization) or 3+.

Adjuvant treatment

According to clinical practice in the Netherlands, all cases were individually discussed in a multidisciplinary meeting before and after salvage mastectomy. When appropriate, patients underwent (neo)adjuvant treatment, by either chemotherapy, hormone therapy or re-irradiation.

Definition of outcomes

Patterns of re-recurrence after salvage mastectomy for IBTR were defined as follows: chest wall recurrence (local recurrence, LR), regional recurrence (either in ipsilateral or contralateral axillary lymph nodes [29], periclavicular lymph nodes or parasternal lymph nodes, RR) and distant metastasis (DM). The time to the first occurring event was expressed in months after salvage surgery. Patients alive without recurrent disease at the end of follow-up were censored.

Overall survival was calculated in months after salvage surgery. Patients alive at the end of follow-up were censored.

Statistical analysis

To identify factors associated with multifocality in IBTR, all possible predictor variables were tested using univariate binary logistic regression analysis. Overall and re-recurrence-free survival of patients after salvage mastectomy for IBTR were compared for uni- and multifocal tumors using Kaplan-Meier curves with a log-rank test. Cox-regression analysis was performed to correct for treatment effect on prognosis after unifocal and multifocal IBTR. All statistical analyses were executed using SPSS version 25 (SPSS Inc., Chicago, Illinois, USA). Statistical significance was set at 0.05.

Results

After review, 215/266 patients (81%) were eligible for inclusion (see Fig. 1). Primary breast cancer treatment took place in the period 1980–2013 and the IBTRs were diagnosed and treated in the period 2002–2014. The median time to IBTR was 140 months. Multifocality

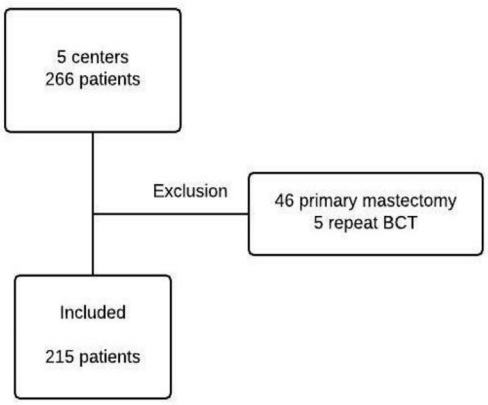

Fig. 1. Selection process.

was found in 50 (22.9%) out of 215 ablative specimens. Table 1 shows the patient and tumor characteristics of the primary tumor preceding the unifocal or multifocal IBTR. Age, hormone receptor and Her2 status and adjuvant therapy choices in primary treatment were not associated with multifocality in IBTR. In Table 2, patient and tumor characteristics of IBTR are compared between patients with unifocal and multifocal IBTR. Age and time to IBTR were not significantly associated with the presence of multifocality. Multifocal IBTRs were associated with a higher chance of axillary positivity (pN+).

There was no significant difference in the use of neoadjuvant treatment in uni- and multifocal IBTR. However, patients with multifocal IBTR were significantly more often treated with adjuvant endocrine therapy and re-irradiation of the breast.

The prognosis after salvage surgery for IBTR, in terms of local and regional re-recurrence, distant metastasis and overall survival compared between patients with unifocal and multifocal IBTR is displayed in Fig. 2. Chest wall recurrences as a first re-recurrence occurred in 19 patients (8.8%), of whom 12 (7.3%) with a unifocal IBTR and 7 (14.0%) after a multifocal IBTR ($p = 0.120$). Regional recurrences as a first event after IBTR occurred in 16 patients (7.4%), of whom 13 (7.9%) after a unifocal IBTR and 3 (6%) in the multifocal IBTR group ($p = 0.773$). In 37 patients (17.2%) the first recurrence after IBTR was distant metastasis, of which 25 (15.2%) in the unifocal IBTR group and 12 (24%) in the multifocal IBTR group ($p = 0.122$).

After a median follow-up of 63 months, 177 (82.3%) patients were alive with a mean overall survival of 128 months. Comparing overall survival for patients with unifocal and multifocal IBTR, no significant difference was found (84.2% of patients with unifocal IBTR, mean survival 132 months vs. 76.0% of patients with multifocal IBTR, mean survival 112 months, $p = 0.197$).

As multifocal tumors were treated significantly more often with adjuvant radiotherapy and endocrine therapy (Table 2), multivariable Cox regression analyses were performed correcting for these factors in the prognostic impact of multifocal IBTR. This showed no difference in terms of local and regional recurrence, distant metastasis or overall survival (Table 3).

Discussion

To our knowledge, this is the first study to report on the risk of multifocality in IBTR. As the standard of care in case of IBTR has always been salvage mastectomy, insight in this topic was of less importance than in primary treatment, where BCT has become the treatment of first choice in the majority of patients. However, with a growing interest for repeat BCT in selected patients with IBTR, it became important to know more about the prevalence and predictors of multifocality in these patients.

This multicenter retrospective cohort study included 215

Table 1
Tumor and patient characteristics of *primary* tumor associated with multifocality in IBTR.

	Unifocal IBTR (n = 165)	Multifocal IBTR (n = 50)	OR	95%-CI OR	p	
Age (years; median + range)	51 (26–80)	49 (32–84)	1.00	0.97–1.03	0.821	
Tumor size (mm)[a]	14.95	16.94	1.04	0.99–1.10	0.132	
Tumor type						
DCIS	8 (4.8%)	4 (8.0%)			0.191	DCIS vs invasive
IDC	112 (67.9%)	26 (52.0%)			0.422	IDC vs ILC
ILC	16 (9.7%)	2 (4.0%)				
Unknown	29 (17.6%)	18 (36.0%)				
Tumor grade (Bloom & Richardson)						
I	20 (12.1%)	8 (16.0%)	(ref)			
II	33 (20.0%)	8 (16.0%)	0.61	0.96–73.36	0.384	
III	21 (12.7%)	1 (2.0%)	0.12	0.01–1.04	0.054	
Unknown	91 (55.2%)	33 (66.0%)				
Estrogen receptor status						
Positive	80 (48.5%)	16 (32.0%)			0.727	
Negative	19 (11.5%)	3 (6.0%)				
Unknown	66 (40.0%)	31 (62.0%)				
Progesterone receptor status						
Positive	66 (40.0%)	14 (28.0%)			0.863	
Negative	26 (15.8%)	5 (10.0%)				
Unknown	73 (44.2%)	31 (62.0%)				
Her2Neu receptor status						
Positive	4 (2.4%)	3 (6.0%)			0.103	
Negative	46 (27.9%)	8 (16.0%)				
Unknown	115 (69.7%)	39 (78.0%)				
Adjuvant radiotherapy						
Yes	160 (98.2%)	49 (98.0%)			0.942	
No	3 (1.8%)	1 (2.0%)				
Unknown	2 (0.9%)	–				
Adjuvant chemotherapy						
Yes	28 (17%)	8 (16.0%)			0.979	
No	128 (77.6%)	39 (78.0%)				
Unknown	9 (5.5%)	3 (6.0%)				
Adjuvant endocrine therapy						
Yes	24 (14.5%)	8 (16.0%)			0.836	
No	134 (81.2%)	39 (78.0%)				
Unknown	7 (4.2%)	3 (6.0%)				
pN						
0	116	37			0.213	
1	26	7				
2	1	2				
x	22	4				

[a] Size of the largest focus.

Table 2
Tumor and patient characteristics of IBTR associated with multifocality.

	Unifocal IBTR (n = 165)	Multifocal IBTR (n = 50)	OR	95%-CI OR	p	
Age (years; median + range)	65 (32–84)	66 (34–87)	1.02	0.99–1.05	0.286	
Tumor size (mm)[a]	17.61	17.74	1.00	0.97–1.04	0.935	
Tumor type						
DCIS	11 (6.7%)	3 (6.0%)			0.832	DCIS vs invasive
IDC	129 (78.2%)	39 (78.0%)			0.501	IDC vs ILC
ILC	14 (8.5%)	6 (12.0%)				
Unknown	11 (6.7%)	2 (4.0%)				
Tumor grade (Bloom & Richardson)						
I	32 (19.8%)	10 (21.3%)	(ref)			
II	75 (46.3%)	23 (48.9%)	0.97	0.42–2.30	0.965	
III	55 (34.0%)	14 (29.8%)	0.82	0.32–2.05	0.662	
Unknown	3 (1.4%)	3 (1.4%)				
Estrogen receptor status						
Positive	119 (72.1%)	41 (82.0%)			0.102	
Negative	33 (20.0%)	5 (10.0%)				
Unknown	13 (7.9%)	4 (8.0%)				
Progesterone receptor status						
Positive	99 (60.0%)	31 (62.0%)			0.777	
Negative	53 (32.1%)	15 (30.0%)				
Unknown	13 (7.9%)	4 (8.0%)				
Her2Neu receptor status						
Positive	17 (10.3%)	5 (10.0%)			0.989	
Negative	135 (81.8%)	40 (80.0%)				
Unknown	13 (7.9%)	5 (10.0%)				
Time to recurrence (mean, months)	138.51	164.82	1.00	1.00–1.01	0.054	
Time to recurrence						
>2 years			(ref)			
<2 years			0.90	0.31–2.56	0.845	
Neoadjuvant treatment						
Chemotherapy	1 (0.6%)	1 (0.6%)				
Endocrine therapy	1 (0.6%)	1 (2.0%)				
None	155 (93.9%)	45 (90.0%)				
Unknown	8 (4.8%)	3 (6.0%)				
Adjuvant radiotherapy						
Yes	12 (7.3%)	14 (28.0%)			*<0.000*	
No	153 (92.7%)	36 (72.0%)				
Adjuvant chemotherapy						
Yes	43 (26.1%)	15 (30.0%)			0.582	
No	122 (73.9%)	35 (70.0%)				
Adjuvant endocrine therapy						
Yes	90 (54.5%)	38 (76.0%)			*0.007*	
No	75 (45.5%)	12 (13.8%)				
pN						
0	90 (41.7%)	15 (30.0%)			*0.001*	
1	13 (6.0%)	10 (20.0%)				
2	0 (0.0%)	0 (0.0%)				
x	103 (47.7%)	25 (50.0%)				

[a] Size of the largest focus.

patients with IBTR. The prevalence of multifocality was 22.9%, which is considerably higher than the figures reported for primary breast cancer, approximately 10% [1]. This could be an expression of unfavorable primary tumor characteristics, which are associated with a higher risk of IBTR [30], but in this study, no prognostic factors could be identified. According to literature, IBTRs can be divided in 'true' recurrences (TR) and new primary tumors (NPT) [31–33], of which the latter appear to have a better survival [31,34,35]. A reliable distinction between TR and NPT can be of great importance in decision-making in case of IBTR, as an NPT could theoretically be regarded as primary breast cancer and thus be treated as such. The higher prevalence of multifocality in IBTR leads to the hypothesis that multifocal IBTRs represent, more often than unifocal ones, a TR rather than an NPT. To date, there is no consensus on the most reliable method to differentiate between TR and NPT. Some rely on tumor characteristics alone, for example tumor type, location of recurrence, time to recurrence, involved margins after primary surgery and receptor status. Others go further by using molecular analysis to investigate the clonality between the primary tumor and IBTR [33]. However, until date no studies have been published regarding the clinical significance of clonality testing by comparing outcomes between clonally related and non-clonally related IBTRs to substantiate this hypothesis. In this study, data regarding the differentiation between TR and NPT were very limited and could therefore unfortunately not be added to the analysis. Future studies to investigate the clinical significance of differentiating between TR and NPT, and which method is the most reliable, are needed.

Even though the prevalence of multifocality in IBTR is higher than in primary breast cancer, the findings in this study imply that more than 75% of patients could technically be feasible for repeat BCS, in line with preceding studies investigatingrepeat BCT for IBTR, excluding all multifocal tumors [23–26]. We would like to propose that multifocality per se does not have to be a technical contraindication for repeat BCS as long as the foci are within surgically workable boundaries and the size of the breast allows for repeat BCS. The axillary positivity associated with multifocal IBTR is in line with literature, at least for primary breast cancer [36]. Recently, Dihge et al. published a similar study identifying (among other factors) multifocality as a predictor for axillary involvement

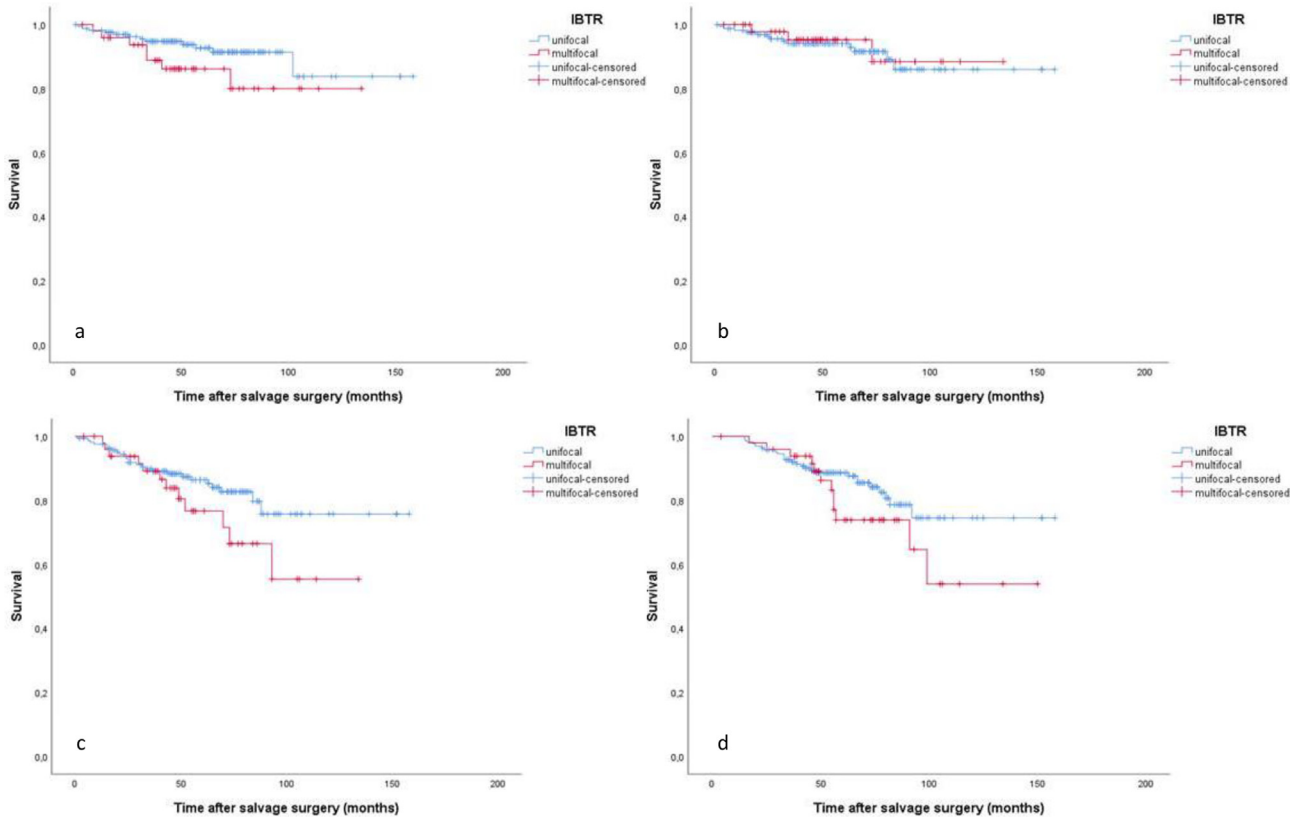

Fig. 2. Patterns of first re-recurrence and overall survival after salvage mastectomy for unifocal and multifocal IBTR. a: chest wall recurrences b: regional re-recurrences c: distant metastasis d: overall survival.

Table 3
Univariate and multivariable Cox regression analyses of factors influencing overall survival after IBTR.

Factor	Local recurrence	p	Regional recurrence	p	Distant metastasis	p	Overall survival	p
	HR (95%-CI)		HR (95%-CI)		HR (95%-CI)		HR (95%-CI)	
Unifocal vs. multifocal	1.957 (0.704–5.443)	0.198	0.799 (0.194–3.301)	0.757	1.090 (0.487–2.440)	0.834	1.070 (0.489–2.343)	0.865
Adjuvant ET	1.461 (0.405–5.264)	0.562	0.347 (0.105–1.146)	0.083	1.220 (0.532–2.798)	0.638	0.772 (0.381–1.567)	0.474
Adjuvant RT	2.007 (0.634–6.356)	0.236	5.008 (1.099–22.83)	0.037	2.670 (1.102–6.468)	0.030	2.195 (0.899–5.359)	0.084

Abbreviations: HR hazard ratio, CI confidence interval, ET endocrine therapy, RT radiotherapy.

[37]. This would suggest that the axillary positivity found in this study is not predictive of, but rather a result of multifocal disease.

Our findings suggest an inferior local control of multifocal IBTR, even after salvage mastectomy (14% chest wall recurrences as opposed to 7% after unifocal IBTRs, not statistically significant). The differences are smaller for regional re-recurrence and distant metastasis. The latter implies that multifocality does not have a high prognostic impact on survival-determining outcomes and that therefore, when technically feasible, repeat BCS could be considered for multifocal tumors as part of a multimodality treatment.

The retrospective nature of this study, resulting in missing data, and the increasing efficacy of primary BCT, resulting in a small sample size, could explain the lack of significant results in this analysis. Another limitation may be related to the sampling of the mastectomy specimens by using slices of 10 mm. This could have resulted in an underestimation of the prevalence of multifocality, as lesions smaller than 10 mm may have been missed. Furthermore, observer bias could have been of influence, as multifocality screening in ablative specimens was not standard practice during the greatest part of this study period. It is possible that in several cases, the suspicion for multifocality was already raised during the preoperative workup and that the pathologist was alerted via the pathology request form. Of all imaging performed before surgery, an MRI was done in only 4 cases with multifocal tumors. It is known that MRI is a sensitive technique to detect multifocality in primary breast cancer [38]. It would be interesting to establish the additional value of MRI in the preoperative workup of patients with IBTR to identify those who are eligible for repeat BCT.

Conclusion

Multifocality is present in almost one out of four patients with IBTR. This high prevalence is important to keep in mind when considering repeat BCT. . Axillary positivity (pN+) seems to be associated with multifocality. This study did not identify any prognostic factors for multifocality in IBTR.

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None.

Declaration of competing interest

The authors declare that there is no conflict of interest.

CRediT authorship contribution statement

Coco J.E.F. Walstra: Conceptualization, Methodology, Validation, Investigation, Writing - original draft, Visualization, Data curation. **Robert-Jan Schipper:** Conceptualization, Methodology, Validation, Writing - original draft, Writing - review & editing. **Ingrid G.M. Poodt:** Data curation, Writing - review & editing. **Adriana J.G. Maaskant-Braat:** Resources, Writing - review & editing. **Ernest J.T. Luiten:** Resources, Writing - review & editing. **Marie-Jeanne T.F.D. Vrancken Peeters:** Resources, Writing - review & editing. **Marjolein L. Smidt:** Resources, Writing - review & editing. **Ellen Degreef:** Writing - review & editing. **Adri C. Voogd:** Methodology, Writing - review & editing. **Grard A.P. Nieuwenhuijzen:** Conceptualization, Validation, Supervision, Writing - review & editing.

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