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Impact of margin distance on recurrence and survival following breast-conserving surgery after neoadjuvant systemic therapy

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Current evidence does not support the application of "no-ink-on-tumor" negative margins following breast-conserving surgery (BCS) in breast cancer (BC) patients who have received neoadjuvant systemic treatment (NST). We compared loco-regional free survival (LRFS), disease-free survival (DFS), and overall survival (OS) based on different tumor margin distance thresholds in a cohort of 235 BC patients treated with NST and subsequent BCS between 01/2015 and 12/2019. The 5-year LRFS was 81.6% in patients with "no-ink-on-tumour", margins and 71.0% in those with positive margins ($p = 0.584$). Margins >1 mm were associated with superior outcomes, with a 5-year LRFS of 84.0% compared to 69.3% in patients with margins ≤1 mm ($p = 0.005$). Additionally, margins >1 mm were significantly correlated with longer DFS ($p = 0.028$) and OS ($p = 0.001$). These findings suggest that a surgical margin distance >1 mm provides the best LRFS, DFS, and OS outcomes for this group of BC patients.

The incidence of breast cancer (BC) is increasing and has surpassed lung cancer as the most common cancer among women. Fortunately, mortality rates are decreasing due to early detection and treatment[1,2]. One important treatment advance has been the introduction of neoadjuvant systemic treatment (NST) for patients diagnosed with BC[2,3]. Previously, the primary objective of NST was to reduce tumour size, enabling breast-conserving surgery (BCS) and avoiding mastectomy[3–7]. NST is now more often used to shrink unresectable tumours and to reduce excision volume in cases that are resectable initially[6–8]. NST has also led to the phenomenon of pathological complete response (pCR), which is associated with a better prognosis for these BC patients[9,10]. The frequency of pCR is increasing, especially with the development of new targeted therapies[10–12]. Another advantage of NST is the ability to evaluate 'in vivo' tumour response and adapt adjuvant treatments accordingly[2,3,12]. Following international recommendations, the use of NST has increased in recent years, and small, aggressive stage I or II tumours are now treated with NST[2,3].

Even for patients treated with NST, BCS remains a first-line indication. Several hypotheses have been proposed regarding the potential advantages of BCS after NST. BCS provides equivalent or better survival compared to mastectomy[13,14], better cosmetic outcomes and quality of life[7,15], and finally fewer positive margins[7,14–17].

However, identifying residual tumours after NST is challenging for surgeons performing BCS. The extent of residual tumour is uncertain and difficult to assess pre- and intraoperatively[12,16,18–20]. Tumour marking is therefore essential to distinguish residual tumours or the tumour bed and ensure clean margins[21]. Negative resection margins are necessary because they have been shown to improve prognosis and reduce the risk of local recurrence in lumpectomy in both primary BCS and also after NST[7,8,14,16,22]. Currently, there is limited data on how to define negative and positive resection margins after BCS following NST[7,14,16,23]. There is no clear evidence that current guidelines for BCS negative margins, defined as "no-ink-on-tumour," apply to patients who have received NST[24–27]. Resection margins

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are a concern, and fears of being too narrow can lead to unnecessary re-excisions or mastectomies. Therefore, it is important to define these margins accurately[25].

The aim of this study was to determine the influence of surgical resection margin distance on loco-regional recurrence (LRR) and survival outcomes in patients with BC treated with BCS after NST.

Results

Patient clinico-pathological characteristics and margin status

During the study period, 235 patients underwent BCS at the IJB after NST and were included in the study. The patient selection process is presented in Fig. 1.

The median age of the patients was 52.9 years (range 27.9–87.7). The tumour was unifocal at presentation for 198 (84.2%) patients and the median tumour size at diagnosis was 30 mm (range 7–75). On initial core biopsy, 216 (91.9%) patients had invasive ductal carcinoma (IDC) and 132 (56.9) patients had high-grade tumours. Breast cancer subtypes included 85 (36.5%) patients with HR+/HER2− disease, 72 (30.9%) with HR+/HER2+ disease, and 58 (24.9%) with HR-/HER2- disease. Most patients received neoadjuvant chemotherapy 215 (91.5%). All 90 (38.3%) HER2+ patients received neoadjuvant trastuzumab, and adjuvant endocrine therapy was prescribed to all 154 (65.5%) HR+ patients. A complete response to NST on MRI was observed in 27.3% of the patients. No residual breast tumour on the final pathology (FP) was observed in 76 (32.5%) patients. Axillary dissection was performed for majority of patients (82.9%) and 230 (97.9%) patients received radiotherapy following surgical management. The clinicopathological and treatment characteristics of the patients are detailed in Table 1.

Margin status

One-stage BCS with a negative margin of "no-ink-on-tumour" was obtained in 214 (91.1%) of patients. Intraoperative re-excision was performed in 94 patients (40.2%). The final margin status was positive ("ink-on-tumour") in 21 (8.9%) patients, for residual invasive disease in 16 (6.8%) patients and only for residual in situ disease in 5 (2.1%) patients. The negative ("no-ink-on-tumour") margins were as follow: "tangent" (≤1 mm) in 26 (11.1%) patients, "close" (1–2 mm) for 17 (7.2%) patients, and "distant" (>2 mm) for 171 (72.8%) patients. For 4 (1.7%) patients with positive margins located posteriorly, an excision was not considered necessary and/or possible by the operating surgeon. A secondary surgery was done in 17 (7.2%) patients, 8 (3.4%) mastectomies and 9 (3.8%) secondary re-excisions. On univariate analysis, pathological T and N stage, histologic type, receptor subtype, and RCB classification were associated with surgical margins >1 mm ($p = 0.05$, Table 2).

Oncological outcomes

The median follow-up for patients included in the study was 63.5 (range 3–109.5) months. There were 25 (10.6%) LRRs in the studied population, 21 (8.9%) breast recurrences and 4 (1.7%) axillary recurrences (3 of them associated with an ipsilateral breast recurrence). LRRs occurred in 3 patients with a "positive" margin, in 9 with a "tangent" margin, in none with a "close" margin, and in 13 with a "distant" margin. A distant recurrence was found in 29 (12.3%) cases. Twenty-six (11.1%) patients died during the follow-up period.

The unadjusted 5-year LRFS was 80.9% (95% CI: 75.6–86.7). Comparing the 5-year LRFS of different margin cut-offs, better LRFS was observed ($p = 0.005$) for patients with margins >1 mm (84.0%; 95% CI: 78.3–90.0) than for those with resection margins ≤1 mm (69.3%; 95% CI: 56.5–85.0) (Fig. 2A). There was a trend towards better LRFS ($p = 0.108$) between patients with margins >2 mm (80.3%; 95% CI: 77.3–89.7) and those with margins ≤2 mm (75.0%; 95% CI: 64.2–87.6) (Fig. 2B). However, we did not observe a significant difference ($p = 0.584$) between negative margins (81.6%; 95% CI: 76.0–87.6) and positive ("ink-on-tumour") margins (71.0%; 95% CI: 52.4–96.3) (Fig. 2C).

Overall 5-year OS for the whole cohort was 88.9% (95% CI: 84.5–93.4) and 5-year DFS was 75.7% (95% CI: 69.8–82.0). A higher 5-year OS rate was observed in patients with margins >1 mm than for those with resection margins ≤1 mm with an absolute difference amount of 12.9% ($p = 0.001$) (Fig. 2D). A trend towards better OS, ($p = 0.044$), was observed in women with margins >2 mm (90.6%; 95% CI: 85.8–95.7) than those with margins ≤2 mm (84.2%; 95% CI: 75.1–94.3) (Fig. 2E). Again, no difference was observed ($p = 0.717$) for 5-year OS between negative margins (88.7%; 95% CI: 84.1–93.6) and positive ("ink-on-tumour") margins (87.8% 95% CI: 73.4–100.0) (Fig. 2F).

There was also a benefit ($p = 0.028$) observed in DFS for margins >1 mm (79.1%; 95% CI: 72.9–85.9) compared to those ≤1 mm (62.1%; 95% CI: 75.1–94.3) (Fig. 2G). No DFS benefit ($p = 0.241$) was observed for margins >2 mm (78.7%) compared to those ≤2 mm (67.8%) (Fig. 2H). There was no DFS difference observed ($p = 0.582$) in women with negative margins (76.7%; 95% CI: 70.7–83.3) compared to those with "positive" margins (65.3%; 95%CI: 46.0–92.6) (Fig. 2I).

In a univariate analysis, after adjusting the proportional hazards regression analysis for age, menopausal status, BMI, presenting clinical T stage, tumour focality, tumour grade on biopsy, ER, PR, HER2, and Ki67 status, intrinsic subtype, response to treatment on MRI, ypN stage, and residual cancer burden (RCB) status, it became apparent that status of RCB0 was associated with an improved LRFS (HR = 0.36; $p = 0.022$; 95% CI: 0.17–0.87), OS (HR = 0.17; $p = 0.016$; 95% CI: 0.04–0.72) and DFS (HR =

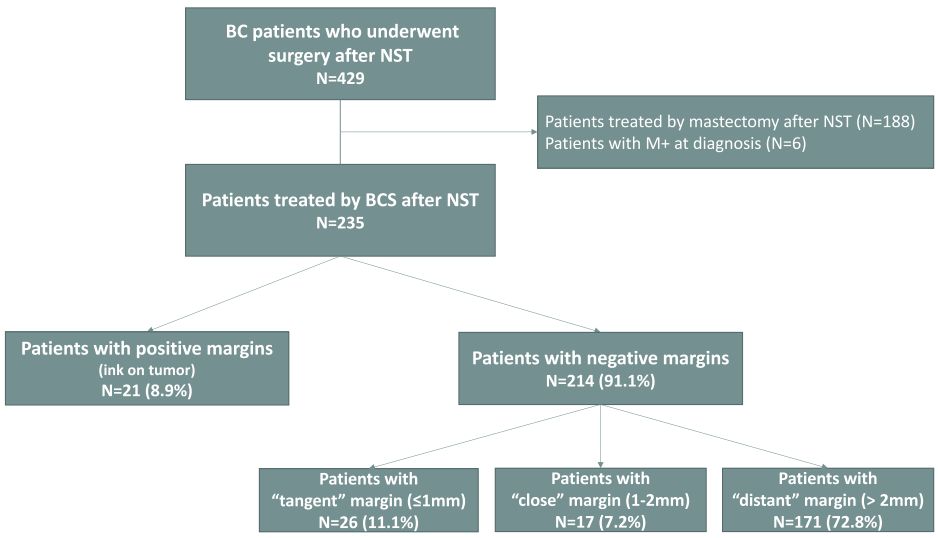

Fig. 1 | Flowchart of patient population selection and categorization according to final pathological margin status. The prospective database was searched for breast cancer (BC) patients treated with neoadjuvant systemic therapy (NST) between 2014 and 2019 at Institut Jules Bordet. After the exclusion of patients treated with mastectomy, and those with metastatic (M+) disease at presentation, only patients who underwent breast-conserving surgery (BCS) were included in the study. The included BC population was categorized according to the final margin status at pathology for different margin distance cut-offs.

Table 1 | Clinical, pathologic, and treatment characteristics of the study population

Variable	*N* (%)
Patients	235
Age median (range)	52.9 (27.9–87.7)
BMI median (range)	25.5 (17.1–45.4)
Clinical T Size (mm) median (range)	30 (7–75)
Clinical N stage	
cN0	81 (34.4%)
cN+	107 (45.5%)
cNx	47 (20%)
Histology[a]	
Ductal	216 (92.3%)
Lobular	10 (4.2%)
Other	8 (3.4%)
Tumour grade[a]	
G1	17 (7.3%)
G2	83 (35.8%)
G3	132 (56.9%)
Ki 67 index[a] median (range)	40% (5–100%)
Intrinsic subtype[b]	
Luminal A	33 (14.0%)
Luminal B	124 (52.8%)
HER2-enriched	18 (7.6%)
Triple-negative	58 (24.7%)
Missing data	2 (0.8%)
Response to NST on MRI	
Complete response	63 (27.3%)
Partial response	141 (61%)
Stable	25 (10.8%)
Progression	2 (0.9%)
Missing data	4 (1.7%)
RCB classification	
0 (pCR)	76 (32.3%)
I	21 (8.9%)
II	107 (45.5%)
III	31 (13.2%)
Pathological size (mm) median, (range)	16 (1–55)
Final nodal stage	
ypN0	168 (71.5%)
ypN1	43 (18.3%)
ypN2-3	20 (8.5%)
Type of axillary surgery	
SLNB	34 (14.5%)
ALND	197 (83.8%)
None	4 (1.7%)
One stage BCS	214 (91.1%)
Secondary breast surgery	17 (7.2%)
Re-excision	9 (3.8%)
Mastectomy	8 (3.4%)
Postoperative RT[c]	230 (97.9%)
Endocrine adjuvant therapy	154 (65.5%)
Follow-up (months)	
median (range)	63.5 (3-109.5)
Local recurrence	21 (8.9%)
Axillary recurrence	4 (1.7%)
Distant metastasis	29 (12.3%)
BC mortality	26 (11.1%)

BC breast cancer, *BMI* body mass index, *T* tumour, *N* node, *G* grade, *ER* oestrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor type 2, *NST* neoadjuvant systemic treatment, *MRI* magnetic resonance imaging, *RCB* residual cancer burden, *pCR* pathologic complete response, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection, *BCS* breast-conserving surgery, *RT* adjuvant whole breast radiotherapy.
[a]On diagnostic biopsy.
[b]Molecular subtype was based on oestrogen receptor (ER) status and human epidermal growth factor receptor 2 (HER2; Erb2-neu) gene amplification and a Ki67 cut-off at 20% at diagnosis.
[c]Regional nodal irradiation was recommended for every case with lymph node invasion identified at diagnosis (cN+) and/or at the final pathological analysis (ypN+).

0.49; $p = 0.032$; 95% CI: 0.25–0.94). While the final positive ypN status was significantly associated with worse OS (HR = 2.8; $p = 0.008$; 95% CI: 1.30–6.07) and DFS (HR = 1.87; $p = 0.025$; 95% CI: 1.08–3.23) but did not have a significant association on LRFS (HR = 1.83; $p = 0.053$; 95% CI: 0.99–3.37).

When different surgical margin distances were included in a multivariate Cox regression model that accounted for baseline tumour characteristics and treatment covariates (Table 3), surgical margins >1 mm remained a significant independent predictor of both LRFS (HR, 0.47; 95% CI, 0.23–0.95; $p = 0.035$) and OS (HR, 0.40; 95% CI, 0.17–0.94; $p = 0.036$). An increased RCB score (>0) was also significantly associated with worse LRFS (HR, 3.03; 95% CI, 1.19–7.70, $p = 0.020$) and OS (HR, 10.53; 95% CI, 1.35–82.25, $p = 0.024$). Additionally, the intrinsic subtype was associated with the risk of loco-regional disease recurrence and DFS (Table 3).

Discussion

The "optimal" resection margin distance after BCS following NST is not yet clearly defined[7,8,16,23–25,27]. In this cohort of BC patients treated with NST followed by BCS, evaluation of various margin definitions suggests that a distance greater than 1 mm should be considered safer for our patients. Resection margins >1 mm offer better 5-year LRFS compared to those ≤1 mm (84.0% versus 69.3%, $p = 0.005$). Furthermore, the advantage of a resection margin distance >1 mm that was observed in this study was also significantly associated with both OS (91.5% versus 78.6%, $p = 0.001$) and DFS (79.1 versus 62.1%, $p = 0.028$) in BC patients who received NST followed by BCS.

Since 2014, for tumours treated with primary BCS, increasing the margin distance has been considered to provide no additional benefit compared to the "no-ink-on-tumour" margin[22,26]. By analogy, this "no-ink-on-tumour" margin has furthermore been considered to also be optimal for BCS cases after NST, but without clear evidence[8,16,23–25,27]. However, a recent review and meta-analysis of 68 studies including 112,140 women treated with upfront BCS reported that a minimum margin of >1 mm was the margin required to minimize both distant recurrence and local recurrence in patients treated even with primary BCS[22].

The "optimal" resection margin distance of BCS following NST is not yet clearly defined[23–25]. A few retrospective studies have sought to identify the most appropriate margin distance in the context of BCS after NST. A wide variety of margin definitions have been tested, but studies have used either a different margin cut-off or a somewhat different methodology, to identify whether the cases with pCR in the breast were taken into account or not. Furthermore, no direct comparison of the margins has been reported according to the "no-ink-on-tumour" definition for this group of patients (Table 4)[4,8,16,23–25,27–29].

Table 2 | Clinicopathologic characteristics according to a resection margin cut-off of 1 mm

Variable	Final margins ≤ 1 mm *N* (%)	Final margins > 1 mm *N* (%)	*P* value
Patients	47 (20%)	188 (80%)	NA
Premenopausal	23 (48.9%)	79 (42.5%)	0.5108
Postmenopausal	24 (51.1%)	107 (57.5%)	
Pathological size (mm), median (IQR)	18.5 (13.0, 26.5)	15.0 (8.0, 21.5)	0.0432
Pathological size[a]			
≤20 mm	24 (51.1%)	90 (47.9%)	0.0900
>20 mm	19 (40.4%)	37 (19.7%)	
No residual invasive tumour[a]	4 (8.5%)	61 (32.4%)	
Histologic type			
Ductal	40 (85.1%)	117 (62.2%)	0.0009
Lobular	1 (2.1%)	6 (3.2%)	
Other[a]	2 (4.3%)	4 (2.1%)	
No residual invasive tumour[a]	4 (8.5%)	61 (32.4%)	
Tumour grade			
G1 & G2	33 (70.2%)	82 (43.6%)	0.2081
G3	7 (14.9%)	33 (17.5%)	
No residual invasive tumour[a]	7 (14.9%)	73 (38.8%)	
Response to NST on MRI			
Complete response	12 (25.5%)	51 (27.7%)	0.8555
No complete response	35 (74.5%)	133 (72.3%)	
Missing data	0	4	
Receptor-based subtype[b]			
HR+ HER2−	20 (43.5%)	65 (34.8%)	0.0362
HR+ HER2+	19 (41.3%)	53 (28.3%)	
HR− HER2−	6 (13.0%)	52 (27.8%)	
HR− HER2+	1 (2.2%)	17 (9.1%)	
Missing data	1	1	
RCB classification			
0	5 (10.6%)	71 (37.8%)	0.0002
I-III	42 (89.4%)	117 (62.2%)	
Histopathological size			
ypT0	4 (8.5%)	61 (32.4%)	0.0006
ypTis	3 (6.4%)	12 (6.4%)	
ypT1	22 (46.8%)	84 (44.7%)	
ypT2	17 (36.2%)	30 (15.9%)	
ypT3	1 (2.1%)	1 (0.5%)	
Nodal status			
ypN0	26 (56.5%)	141 (76.6%)	0.0092
ypN+	20 (43.5%)	43 (23.4%)	
Missing data	1	4	
Intraoperative re-excision			
Yes	21 (44.7%)	73 (39.0%)	0.5084
No	26 (55.3%)	115 (61.1%)	

G grade, *NST* neoadjuvant systemic therapy, *MRI* magnetic resonance imaging, *RCB* residual cancer burden, *ypT* post-neoadjuvant treatment pathological tumour classification, *ypN* post-neoadjuvant treatment pathological nodal classification.

[a]DCIS included.

[b]Receptor-based subtype was based on oestrogen receptor (ER) status and human epidermal growth factor receptor 2 (HER2; Erb2-neu) gene amplification at diagnosis.

The 1 mm margin cut-off has also been studied, but, contrary to our findings, the results of published studies with this margin limit were not significant[8,23,24,29]. Wimmer et al. analysed data for 406 patients treated between 1994 and 2014 and did not observe a significant difference in LRFS, DFS, or OS between patient groups with margins ≤1 mm or >1 mm[23]. Unlike this study, Wimmer et al. did not include in their analysis the cases with true positive margins after BCS (not included in the study) and the cases with a pCR that were analysed separately[23]. We know that pCR is a factor associated with a better overall prognosis for BC patients treated with NST[9,12,27]. This could explain, at least in part, the absence of a significant difference between the two groups in their study[23]. Furthermore, the percentage of LRR is almost the same in our study (10.6%) as that of Wimmer et al. (11.8%), which could mean that only the different grouping of margins and their analysis of patients explains why no difference in survival was highlighted in their cohort[23].

Similarly, Atzori et al., in their study of 151 patients, did not observe a significant difference in LRR among different margin groups (pCR, >1 mm, and <1 mm), but reported that the pCR group had better OS and DFS[8]. Again, the margin distance of 1 mm represents a stratification factor rather than a cut-off, bearing in mind that cases with pCR that have negative margins were analysed separately[8]. A study from Lin et al. reported a trend toward better LRFS for patients with >1 mm resection margins, even if they did not include in their analysis the cases with positive "ink-on-tumour" margins[24].

The probability of having positive margins is influenced by several factors. In the context of BCS following NST, it was observed that tumour size, higher tumour grade, multifocality, positive lymph node status, low SBR grade, lymphovascular invasion, and associated DCIS put patients at higher risk of positive margins[4,28–32]. Tumours with high proliferative potential respond better to chemotherapy and are more likely to achieve a pCR, while larger tumours are at risk of incomplete response and becoming multifocal, increasing the chances of positive margins[4,10,12,28,31]. The results from this study confirm that having a residual tumour after NST increases the probability of having margins ≤1 mm (89.4% vs. 62.2%, $p = 0.0002$).

Most of the studies that have analysed the correlation between margin distance and survival outcomes after BCS following NST have focused on the 2 mm cut-off (Table 4)[4,16,25,27,28,33]. Only one of these studies carried out on a cohort of 257 patients treated in the 80s and 90s, reported that margins ≤2 mm were associated with increased LRR (HR 2.48, $p = 0.04$). Furthermore, LRR was a strong predictor for distant metastases[33]. The effect of resection margins on LRR after BCS following NST was also addressed by Cheun et al. in the largest retrospective series published, including 2803 patients[25]. This study defined a clear margin as >2 mm and a close margin as ≤2 mm. It compared groups consisting of pCR (RpCR) for the first group, clear and close margins together (R0) for the second group, and positive, "ink-on-tumour" margins (R1) for the third group. The RpCR group had better LRFS than the other two.

To the best of our knowledge, this was the only series to have reported a direct comparison between R1 ('ink-on-tumour') and R0 margins, with no statistically significant difference observed neither for LRFS (0.692) nor for DFS (0.338)[25]. Moreover, for the first time, they reported the effect of residual DCIS on resection margins in the RpCR group and found no benefit to LRFS even if there was residual DCIS on final margins ($p = 0.366$)[25]. In contrast, they found that clinical T and N stage, HR status, and histologic grade were significantly associated with LR. Cheun et al. suggested that the relative risk of LRR after NST according to resection margin distance is not necessarily the same as in cases treated with primary BCS, and the definition of "no-tumour-on-ink" should probably be adapted[25]. Our data agree with this because, as we observed in this study, the differences in survival ($p = 0.717$) and recurrence, LRR ($p = 0.584$) or DFS ($p = 0.582$), were not significantly different. Furthermore, none of the previous studies actually demonstrated directly that "no-tumour-on-ink" margins have an influence on patient survival[4,8,16,23–25,27–29]. These findings suggest that the "no-tumour-on-ink" margin standard may not represent the most appropriate surgical threshold for this particular subgroup of BC patients treated by BCS following NST.

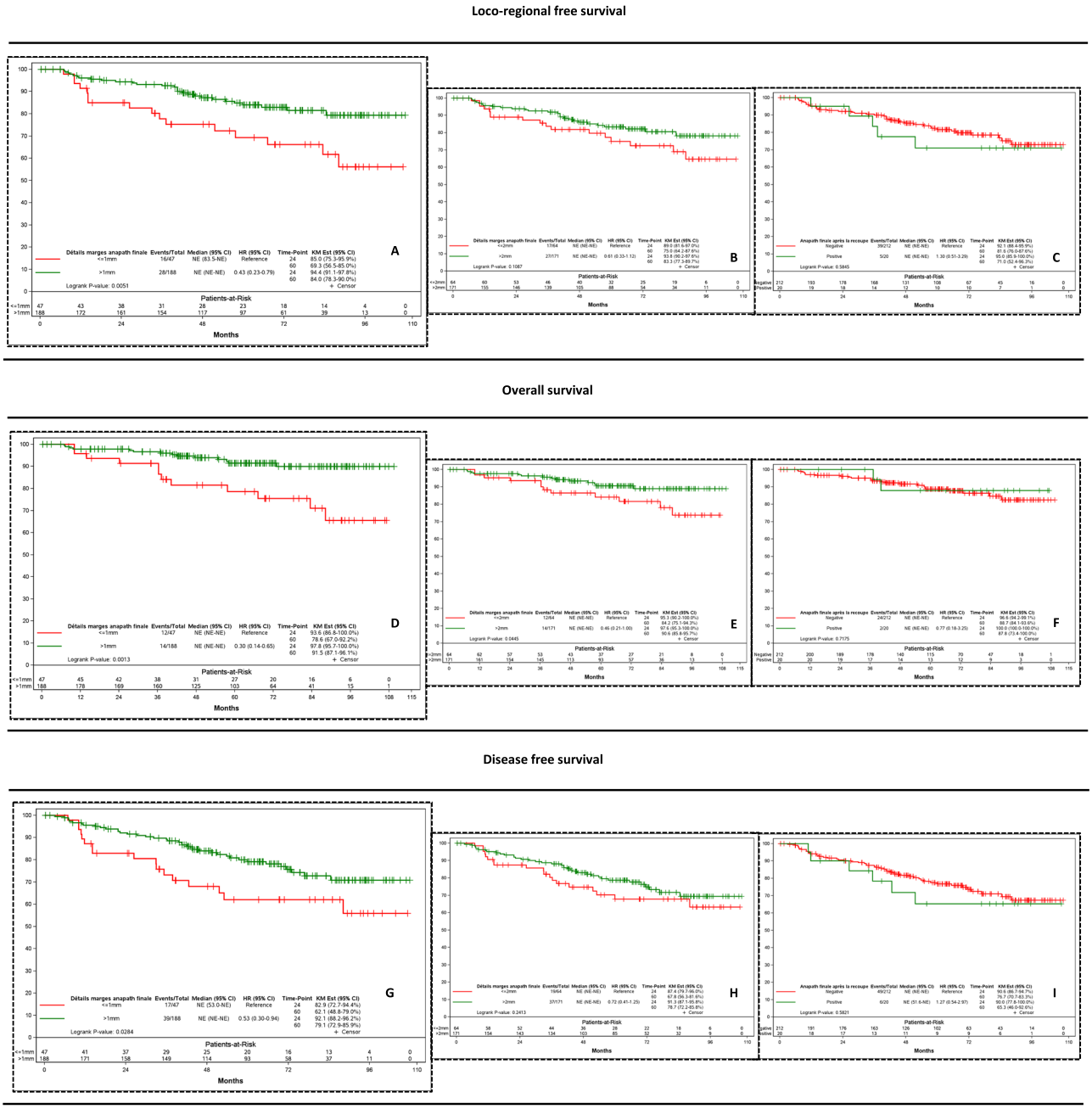

Fig. 2 | Survival curves according to different surgical resection margin distances. The Kaplan–Meier curves show the survival outcomes according to resection margin status. For patients with margins >1 mm, the loco-regional free survival (LRFS) (**A**), overall survival (OS) (**D**) and disease-free survival (DFS) (**G**) was better for those patients with margin widths ≤1 mm. No significant differences were observed for negative and positive ("ink-on-tumour") margins or for LRFS (**C**), OS (**F**), or DFS (**I**). Better OS (**E**) was observed for patients with margins >2 mm compared to those ≤2 mm, but not for LRFS (**B**) or for DFS (**H**).

The data in this study support the idea that the characteristics and biology of the tumour and degree of response to NST, such as pCR, rather than margin resection distance after BCS following NST affects local or distant recurrence and survival in this group of BC patients[12,23–25,27,28,31]. However, considering the increasing number of patients treated with NST and BCS, determining the optimal resection margin for this population must be a priority that cannot be neglected[2,3,7,13,25].

Larger and prospective studies are needed to confirm these results, specifically, our data that show that a resection margin >1 mm is safer for this group of BC patients. Standardization of the definition of resection margins in future studies that address this question of optimal resection margin cut-off (>1 mm) is needed. It is necessary to include in future studies both cases with positive margins, and those with pCR.

The present study is unique in its analysis model of the association of surgical margins distance after BCS following NST on survival outcomes, by focusing on three different cut-off margins of "no-tumour-on-ink", >1 and >2 mm. This consecutive series of patients were treated with contemporary NST, a systematic pretreatment carbon marking of the tumour, and a standardized intraoperative macroscopic pathological margin evaluation was performed in all cases. Nevertheless, the present study has several limitations related primarily to its retrospective, observational, single-institution design and the relatively limited number of patients included. There was a relatively small proportion of patients with a margin between 1 and 2 mm (7.2%) and it is possible that the sample size is insufficient to detect a difference in LRR associated with margin width >1 vs. >2 mm. Our median follow-up is also relatively short, 63.5 months, especially for the

Table 3 | Summary of representative multivariate analysis and their relationship with different survival outcomes

Variable	LRFS Hazard ratio (95% CI)	*P* value	OS Hazard ratio (95% CI)	*P* value	DFS Hazard ratio (95% CI)	*P* value
Final margins status						
≤0 mm	Reference	0.8852	Reference	0.6920	Reference	0.9790
>0 mm	0.93 (0.35–2.50)		1.29 (0.37–4.54)		0.99 (0.94–3.52)	
≤1 mm	Reference	0.0358	Reference	0.0361	Reference	0.1183
>1 mm	0.47 (0.23–0.95)		0.40 (0.17–0.94)		0.60 (0.31–1.14)	
≤2 mm	Reference	0.4222	Reference	0.3517	Reference	0.6598
>2 mm	0.76 (0.39–1.49)		0.67 (0.29–1.55)		0.87 (0.48–1.60)	
Nodal status						
ypN0	Reference	0.1277	Reference	0.0545	Reference	0.0504
ypN+	1.76 (0.85–3.66)		2.40 (0.98–5.84)		1.91 (1.00–3.66)	
RCB classification						
0	Reference	0.0200	Reference	0.0248	Reference	0.0606
I–III	3.03 (1.19–7.70)		10.53 (1.35–82.25)		2.06 (0.97–4.40)	
Intrinsic subtype		0.0245		0.1380		0.0474
Luminal A	Reference	0.2949	Reference	0.4515	Reference	0.1492
Luminal B	1.70 (0.63–4.62)	0.0116	1.55 (0.50–4.80)	0.0665	1.95 (0.79–4.80)	0.0114
HER2-enriched	6.7 (1.53–29.33)	0.0174	5.44 (0.89–33.24)	0.0590	5.47 (1.47–20.42)	0.0214

LRFS locoregional-free survival, *OS* overall survival, *DFS* disease-free survival, *ypN* post-neoadjuvant treatment pathological nodal classification, *RCB* residual cancer burden.

Table 4 | Overview of representative retrospectives studies on interactions between margin width, recurrence, and survival in patients undergoing breast-conserving surgery after neoadjuvant chemotherapy

Authors/Year	Pts	Margin width definition	Follow-up median	LRR (in %)	LRFS (in %)	OS (in %)	DFS (in %)
Rouzier/2001	257[a]	Positive/≤2 mm/>2 mm	93 months	16	15.9/28.6/12.7 $p = 0.04$[a]	NA	NA
Chen/2004	340	≤2 mm vs. >2mm	63 months	9	92 vs. 89, $p = 0.20$	NA	NA
Jwa/2016	335	≤2 mm vs. >2 mm	86.4 months	11	HR 2 $p = 0.21$	NA	NA
Choi/2018	382	≤2 mm/>2 mm/Rx; ≤1 mm vs. >1 mm	57 months	3.9	96.3/94.2/100, $p = 0.37$ NA	91.5/87.8/96, $p = 0.83$ HR 1.11, $p = 0.96$	82.1/82/96, $p = 0.93$ HR 1.13, $p = 0.89$
Wimmer/2019	406[b]	≤1 mm/>1 mm/Rx	84.3 months	11.8	94/91/95; $p = 0.940$	85/88 /96, $p = 0.236$	72/74/87, $p = 0.245$
Lin/2020	161[b]	≤1 mm vs. >1 mm; ≤2 mm vs. >2 mm	47 months	9.9	84.9 vs. 69.5, $p = 0.150$; 85.2 vs. 76.2, $p = 0.335$	NA	NA, $p = 0.162$; NA, $p = 0.414$
Mrdutt/2021	582[b]	≤2 mm vs. >2 mm	39 months	2.4	3 vs. 2 p = NS	7 vs. 2, p = NS[c]	NA, p = NS
Atzori/2022	151	≤1 mm/>1 mm/Rx	46 months	6.6	NA $p = 0.177$	86.2/82.8/ 100, $p = 0.01$	79.3/64.1/ 96.6, $p = 0.002$
Cheun/2022	2803	≤2 mm/>2 mm/Rx; Rx vs. >0 mm; Rx vs. R1; R1 vs. >0 mm	71.2 months	9.3	91.5/94.0/97.4 p = NA HR 2.15, $p = 0.001$ HR 2.55, $p = 0.049$ HR 1.20, $p = 0.692$	NA	NA HR 2.94, $p = 0.001$ HR 3.42, $p = 0.001$ HR 1.17, $p = 0.338$
Di Lena/2024	544[a]	<1 mm/1 mm/≥2 mm	55 months	4.8[a]	88.9/92.2/92.9 $p = 0.78$[a]	81.2/92.6/NA $p = 0.13$	86.6/77.9/80.0 $p = 0.68$
Current study	235	R1 vs. >0 mm; ≤1 mm vs. >1 mm; ≤2 mm vs. >2 mm	63.5 months	10.6	71.0 vs. 81.6, $p = 0.584$; 69.3 vs. 84.0, $p = 0.005$; 75.0 vs. 80.3, $p = 0.108$	87.8 vs. 88.7, $p = 0.717$; 78.6 vs. 91.5, $p = 0.001$; 84.2 vs. 90.6, $p = 0.044$	65.3 vs. 76.7, $p = 0.582$; 62.1 vs. 79.1, $p = 0.028$; 67.8 vs. 78.7, $p = 0.241$

Pts number of patients, *LRR* loco-regional recurrence, *LRFS* loco-regional recurrence-free survival, *DFS* disease-free survival, *OS* overall survival, *NA* not available, *HR* hazard ratio, *Rx* cases with a pCR, *NS* not significant, *R1* ink-on-tumour margin.

[a]Ipsilateral breast tumour recurrence rate.

[b]Cases with positive no-ink-on-tumour margins after initial BCS not included in the study.

[c]Mortality rate.

subgroup of patients with luminal disease that comprises over half of the study population and, with longer follow-up, more recurrences are likely in patients with HR tumours[34]. While this could increase the overall rate of LR, it is likely that those recurrences would occur at the same rate in both margin groups.

In conclusion, our findings suggest that the safest margin distance in patients who undergo BCS after NST is >1 mm. The 5-year LRFS for patients with resection margins >1 mm (91.5%) was better ($p = 0.001$) than for those with margins ≤1 mm (78.4%). Furthermore, a resection margin distance >1 mm was also significantly associated with OS and DFS of BC patients who received NST followed by BCS. However, achieving a pCR remains another important prognostic factor for this group of patients, which must be considered in future studies. Although uncertainty regarding the optimal oncologic margins in this population persists, our findings provide further support for the need to determine safe margins criteria in this population, that could improve survival outcomes for patients treated with BCS following NST.

Methods

Study population and design

This was a retrospective, cohort, exploratory study of patients with invasive BC treated with BCS after NST treatment at the Institut Jules Bordet (IJB), Belgium, over a 5-year period (January 2014–December 2019). The study was conducted in compliance with the Declaration of Helsinki and the General Data Protection Regulation concerning data privacy. The ethics committee of Institut Jules Bordet granted study approval under Reference No. CE3595, dated 26.01.2023. The requirement to obtain patient consent was waived for anonymized, retrospective analysis by the ethics committee.

Inclusion and exclusion criteria

Patients over 18 years of age with invasive BC clinically classified as cT1–T4, cN0–N3, treated with BCS and whole breast radiotherapy (WBR) after NST ((chemotherapy (CT) and/or endocrine therapy (ET)) were included. Patients with invasive BC treated with mastectomy or primary BCS, as well as patients with metastatic or in situ BC were excluded.

Clinical data and procedures

Clinical, pathological, and treatment management data were collected from our prospectively maintained database. Characteristics of the surgical specimen (i.e., margin status and distance, details of re-excisions) and follow-up data (i.e., date of last follow-up, date of death or recurrence, and type of recurrence) were also collected from IJB's computerized medical records. For each patient, the information was collected in a database previously set up on REDCap (Research Electronic Data Capture, Vanderbilt University, USA).

Study evaluation criteria

Data for margin widths were collected as reported on the final pathology on the breast surgical specimen (BSS) of the first one-stage BCS following NST. The standard pathological protocol for evaluating pathological margins at the IJB is as follows: after lumpectomy, the BSS, oriented by the surgeon in the operating room, is inked and then sliced into 3–4 mm-thick sections for pathological analysis of the six margins (upper, lower, anterior, posterior, internal, and external). The smallest distance between the tumour edge and an inked normal tissue margin is measured microscopically. An involved margin is defined as the presence of invasive disease at the inked resection margin, whereas uninvolved margins are reported with the exact distance specified in millimeters. The resection margin was then grouped as follows: positive margin ("ink-on-tumour"), "tangent" margin (≤1 mm), "close" margin (>1–≤2 mm), and "distant" margin (>2 mm). This margin width distance was used for analysis (Fig. 1). The primary endpoint measures were locoregional-free survival (LRFS), overall survival (OS), and disease-free survival (DFS). LRR is defined as local and/or regional (axillary) recurrence. The event-free interval for LRFS and DFS was defined as the time between the date of surgery and the date of any first local and/or regional and/or distant recurrence. Data on follow-up were collected until April 30, 2023.

Statistical analysis

Descriptive statistics are used to summarize the clinical characteristics of the cohort, patient, and tumour. Nominal and/or categorical variables are reported as frequencies and proportions. Continuous variables are reported as means, medians, and interquartile ranges.

The chi-square test was used to compare categorical variables between the two groups with different margins. For continuous variables, the Wilcoxon test was used to compare two distinct groups and the Kruskal–Wallis test was used for continuous variables to compare more than two groups.

The Kaplan–Meier method was used to estimate survival (LRFS, OS, and DFS), with the log-rank test comparing different groups. A Cox model was used to determine the most appropriate resection margin distance threshold. The Cox model was also employed for univariate and multivariate analyses of various prognostic factors. Statistical analysis was performed using SAS software, version 9.4.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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References

1. Bray, F. et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **74**, 229–263 (2024).
2. Loibl, S. et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann. Oncol.* **35**, 159–182 (2024).
3. Curigliano, G. et al. Understanding breast cancer complexity to improve patient outcomes: the St. Gallen International Consensus Conference for the Primary Therapy of Individuals with Early Breast Cancer 2023. *Ann. Oncol.* **34**, 970–986 (2023).
4. Chen, A. M. et al. Breast conservation after neoadjuvant chemotherapy: the MD Anderson Cancer Center experience. *J. Clin. Oncol.* **22**, 2303–2312 (2004).
5. Mo, H. et al. Actual conversion rate from total mastectomy to breast conservation after neoadjuvant chemotherapy for stages II–III breast cancer patients. *J. Breast Dis.* **5**, 51–56 (2017).
6. Mamounas, E. et al. Neoadjuvant systemic therapy for breast cancer: factors influencing surgeons' referrals. *Ann. Surg. Oncol.* **23**, 3510–3517 (2016).
7. Volders, J. H. et al. Breast-conserving surgery following neoadjuvant therapy-a systematic review on surgical outcomes. *Breast Cancer Res. Treat.* **168**, 1–12 (2018).
8. Atzori, G. et al. "*No Ink on Tumor*" in breast-conserving surgery after neoadjuvant chemotherapy. *J. Pers. Med.* **12**, 1031 (2022).
9. von Minckwitz, G. et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J. Clin. Oncol.* **30**, 1796–1804 (2012).
10. Cortazar, P. et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet* **384**, 164–172 (2014).
11. Nanda, R. et al. Effect of pembrolizumab plus neoadjuvant chemotherapy on pathologic complete response in women with early-stage breast cancer: an analysis of the ongoing Phase 2 adaptively Randomized I-SPY2 trial. *JAMA Oncol.* **6**, 676–684 (2020).
12. Agostinetto, E. et al. Post-neoadjuvant treatment strategies for patients with early breast cancer. *Cancers (Basel)* **14**, 5467 (2022).
13. He, X., Ji, J., Qdaisat, A., Esteva, F. J. & Yeung, S. J. Long-term overall survival of patients who undergo breast-conserving therapy or mastectomy for early operable HER2-Positive breast cancer after preoperative systemic therapy: an observational cohort study. *Lancet Reg. Health Am.* **32**, 100712 (2024).

14. Mukhtar, R. A. et al. Breast conservation surgery and mastectomy have similar locoregional recurrence after neoadjuvant chemotherapy: results from 1462 patients on the prospective, Randomized I-SPY2 Trial. *Ann. Surg.* **278**, 320–327 (2023).
15. Diao, K. et al. Patient-reported quality of life after breast-conserving surgery with radiotherapy versus mastectomy and reconstruction. *Ann. Surg.* **278**, e1096–e1102 (2023).
16. Choi, J. et al. Margins in breast-conserving surgery after neoadjuvant therapy. *Ann. Surg. Oncol.* **25**, 3541–3547 (2018).
17. Woeste, M. R., Bhutiani, N., Donaldson, M., McMasters, K. M. & Ajkay, N. Evaluating the effect of neoadjuvant chemotherapy on surgical outcomes after breast conserving surgery. *J. Surg. Oncol.* **123**, 439–445 (2021).
18. Scheel, J. R. et al. MRI, clinical examination, and mammography for preoperative assessment of residual disease and pathologic complete response after neoadjuvant chemotherapy for breast cancer: ACRIN 6657 Trial. *AJR Am. J. Roentgenol.* **210**, 1376–1385 (2018).
19. Drisis, S. et al. Quantitative DCE-MRI for prediction of pathological complete response following neoadjuvant treatment for locally advanced breast cancer: the impact of breast cancer subtypes on the diagnostic accuracy. *Eur. Radiol.* **26**, 1474–1484 (2016).
20. Rajan, K. K. et al. Optimizing surgical strategy in locally advanced breast cancer: a comparative analysis between preoperative MRI and postoperative pathology after neoadjuvant chemotherapy. *Breast Cancer Res. Treat.* **203**, 477–486 (2024).
21. Jha, C. K., Johri, G., Singh, P. K., Yadav, S. K. & Sinha, U. Does tumor marking before neoadjuvant chemotherapy helps achieve better outcomes in patients undergoing breast conservative surgery? A systematic review. *Indian J. Surg. Oncol.* **12**, 624–631 (2021).
22. Bundred, J. R. et al. Margin status and survival outcomes after breast cancer conservation surgery: prospectively registered systematic review and meta-analysis. *Br. Med. J.* **378**, e070346 (2022).
23. Wimmer, K. et al. Impact of surgical margins in breast cancer after preoperative systemic chemotherapy on local recurrence and survival. *Ann. Surg. Oncol.* **27**, 1700–1707 (2020).
24. Lin, J. et al. Association of surgical margins with local recurrence in patients undergoing breast-conserving surgery after neoadjuvant chemotherapy. *BMC Cancer* **20**, 451 (2020).
25. Cheun, J. H. et al. Surgical margin status and survival outcomes of breast cancer patients treated with breast-conserving surgery and whole-breast irradiation after neoadjuvant chemotherapy. *Breast Cancer Res. Treat.* **194**, 683–692 (2022).
26. Moran, M. S. et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *Ann. Surg. Oncol.* **21**, 704–716 (2014).
27. Mrdutt, M. et al. Margin width and local recurrence in patients undergoing breast conservation after neoadjuvant chemotherapy. *Ann. Surg. Oncol.* **29**, 484–492 (2022).
28. Jwa, E. et al. Locoregional recurrence by tumor biology in breast cancer patients after preoperative chemotherapy and breast conservation treatment. *Cancer Res. Treat.* **48**, 1363–1372 (2016).
29. Di Lena, É et al. Impact of margin status on local recurrence in patients with breast cancer undergoing breast-conserving surgery after neoadjuvant chemotherapy: a retrospective Multi-Institutional Cohort Study. *Ann. Surg. Oncol.* **31**, 6786–6794 (2024).
30. Ivanovic, N. et al. Changing the role of pCR in breast cancer treatment —an unjustifiable interpretation of a good prognostic factor as a "factor for a good prognosis". *Front. Oncol.* **13**, 1207948 (2023).
31. Davoine, E. et al. Predictive factors associated with involved margins in breast cancer treated with neoadjuvant chemotherapy followed by breast-conserving therapy. *J. Gynecol. Obstet. Hum. Reprod.* **48**, 467–472 (2019).
32. Zhang, Y. et al. Pathologic evaluation of lumpectomy resection margins for invasive breast cancer: a single institution's experience. *Int. J. Clin. Exp. Pathol.* **16**, 40–47 (2023).
33. Rouzier, R. et al. Primary chemotherapy for operable breast cancer: incidence and prognostic significance of ipsilateral breast tumor recurrence after breast-conserving surgery. *J. Clin. Oncol.* **19**, 3828–3835 (2001).
34. Pedersen, R. N. et al. The incidence of breast cancer recurrence 10–32 years after primary diagnosis. *J. Natl Cancer Inst.* **114**, 391–399 (2022).

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Author contributions

C.F.P., C.O. and I.V. were responsible for the study conception and project administration. P.K., C.O., M.L., E.D.A., I.V. and C.F.P. were responsible for the study methodology. F.D.N., A.D., C.K., D.L., E.D.A., C.F.P. and I.V. contributed to resources. C.O., M.L., P.K. and C.F.P. contributed to data collection. C.O., P.K. and C.F.P. contributed to data analysis. C.F.P., C.O., and I.V. were responsible for manuscript writing. All authors contributed to the revision of the manuscript and approval of the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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