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ORIGINAL ARTICLE

Poor response at restaging MRI and high incomplete resection rates of locally advanced mucinous rectal cancer after chemoradiation therapy

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Abstract

Aim: Mucinous carcinoma is a histological subtype of rectal cancer and has been associated with a poor response to neoadjuvant chemoradiotherapy (CRT). The primary aim of this study was to analyse the response on MRI of mucinous locally advanced rectal cancer (LARC) after CRT compared to regular adenocarcinoma.

Method: Patients with LARC (defined as cT4 and/or cN2), who underwent CRT followed by restaging MRI and surgery in two tertiary referral hospitals were retrospectively included in the study. Pre- and post-treatment MRI was reviewed by an experienced abdominal radiologist.

Results: A total of 102 patients, of whom 29 were diagnosed with mucinous carcinoma, were included for analysis. At restaging MRI, adenocarcinoma patients demonstrated significantly less clinical involvement of the mesorectal fascia (37% vs. 62%, $P = 0.003$) while this was not demonstrated in mucinous carcinoma patients (86% vs. 97%, $P = 0.16$). Significant downstaging after CRT in adenocarcinoma patients ($P = 0.01$) was seen while, in mucinous carcinoma patients, no downstaging after CRT ($P = 0.89$) was seen. Pathology revealed significantly higher rates of an involved circumferential resection margin in mucinous carcinoma versus adenocarcinoma patients (27.6% vs. 1.4%; $P < 0.001$). After multivariate regression analysis, mucinous carcinoma remained an independent prognostic factor for local recurrence (hazard ratio 3.6; 95% CI 1.1–12.4), although no differences in overall or disease-free survival were observed.

Conclusion: Mucinous rectal carcinoma is associated with a poor clinical response at restaging MRI after CRT, leading to relatively higher rates of involved circumferential resection margins at pathology. In this cohort, mucinous carcinoma seems to be a prognostic factor for increased risk of local recurrence, without an effect on overall survival.

KEYWORDS
rectal cancer, neoadjuvant treatment, chemoradiotherapy, response evaluation, MRI, mucinous rectal cancer, locally advanced

All of the listed authors meet the criteria for being an author.

INTRODUCTION

Locally advanced rectal cancer (LARC) is characterized by a threatened or involved mesorectal fascia (MRF) and/or an advanced lymph node staging [1]. Treatment generally consists of preoperative chemoradiotherapy (CRT) followed by surgery [2]. The aim of preoperative treatment is downstaging and downsizing to improve resectability of the tumour [3].

Rectal cancers can be classified according to their histological subtype. The vast majority of rectal cancers consist of adenocarcinoma not otherwise specified. Approximately 10% of rectal cancers are mucinous carcinomas characterized by extensive extracellular mucin that forms more than half of the tumour volume [4].

Mucinous carcinoma has been associated with a poor response to preoperative therapies, compared with adenocarcinoma [5-7]. Previously, Hugen et al. found a higher rate of positive circumferential resection margin (CRM) following CRT for mucinous carcinoma compared with adenocarcinoma, although this did not result in a worse overall survival.

MRI is considered to be the gold standard for primary rectal cancer staging with accuracy rates varying from 66% to 88% [8-10]. Using high resolution imaging, tumour response and potential MRF involvement can be evaluated after neoadjuvant treatment [11,12]. In the preoperative surgical planning process, these MRI findings may help to minimize the risk of an involved CRM [12]. Whether restaging can be performed reliably in mucinous carcinoma patients and as such improve the preoperative surgical plan is unknown. Actual tumour size reduction and response after preoperative CRT of mucinous carcinoma measured at restaging MRI has not been described before.

The primary aim of this study was to analyse the response of mucinous carcinoma compared with adenocarcinoma in LARC patients undergoing preoperative CRT using MRI. We hypothesize that the response in mucinous carcinoma patients is worse compared with adenocarcinoma patients in terms of tumour regression on MRI and clinical MRF involvement. As a secondary aim, findings are correlated with data on CRM involvement at pathology and oncological outcome.

What does this paper add to the literature?

Mucinous rectal cancer has been associated with poor pathological response to preoperative treatment; however, response at restaging MRI has not been reported before. The present study reports on tumour response after neo-adjuvant treatment for mucinous and non-mucinous rectal cancers and assesses the relation with oncological outcomes.

METHODS

Patients

Patients with LARC treated between 2002 and 2014 were collected retrospectively from two tertiary referral hospitals in the Netherlands (Radboud University Medical Centre, Nijmegen, and Catharina Hospital, Eindhoven). Tumours were defined as LARC when they met the following inclusion criteria: histologically proven mucinous adenocarcinoma or adenocarcinoma of the rectum, locally advanced disease (cT4 and/or cN2). All patients underwent long-course preoperative CRT, pre- and post-CRT MRI. Metastatic disease was assessed using CT thorax-abdomen. Patients with metastatic disease, recurrent rectal cancer and those lacking pre-treatment MRI assessment or follow-up data were excluded from the study cohort. Patients were defined as mucinous carcinoma or adenocarcinoma according to the pre-treatment MRI, in order to avoid erroneous classification of tumours with a colloid response following CRT as mucinous carcinoma [13-17].

Patients had regular follow-up after surgery according to the Dutch guidelines, consisting of frequent (3–6 months' interval) carcinoembryonic antigen level measurement and abdominal ultrasound or CT. Local recurrence was diagnosed via imaging (CT or MRI) and/or colonoscopy. Patients with follow-up shorter than 3 months were excluded from recurrence and survival analysis.

Ethical approval for this study was waived by the local medical ethics committee.

Magnetic resonance imaging

An anonymous database was used to collect all MRIs. All pre- and post-CRT images were reviewed by a dedicated abdominal radiologist in rectal cancer staging (SvK). The radiologist was blinded to the clinical data and pathology reports. A standardized scoring form, derived from the European Guidelines for Magnetic Resonance Imaging from the European Society of Gastrointestinal Abdominal Radiology guidelines, was used to review the images [18]. The scoring form contained the following items: distance to anal verge, maximum diameter measured in the axial dimension, histological aspect of the tumour, stage assessed by MRI and malignant features of lymph nodes. MRF involvement was defined using MRI at baseline and after CRT at restaging. Differentiation between mucinous rectal cancer and adenocarcinoma was made by high-resolution T2-weighted imaging [19,20]. For example, Figure 1 shows T2-weighted images of a mucinous rectal cancer and an adenocarcinoma. Downstaging on MRI after CRT was measured and compared with pathological examination. A response was defined as 'significant' if a tumour size reduction or fibrosis of the tumour of >75% was seen. The MRF was defined as 'involved' if the distance between the MRF and tumour was ≤1 mm. Diffusion-weighted MRI was not available in most cases. A clinical complete response was established if no residual tumour and no suspicious lymph nodes were seen at restaging MRI.

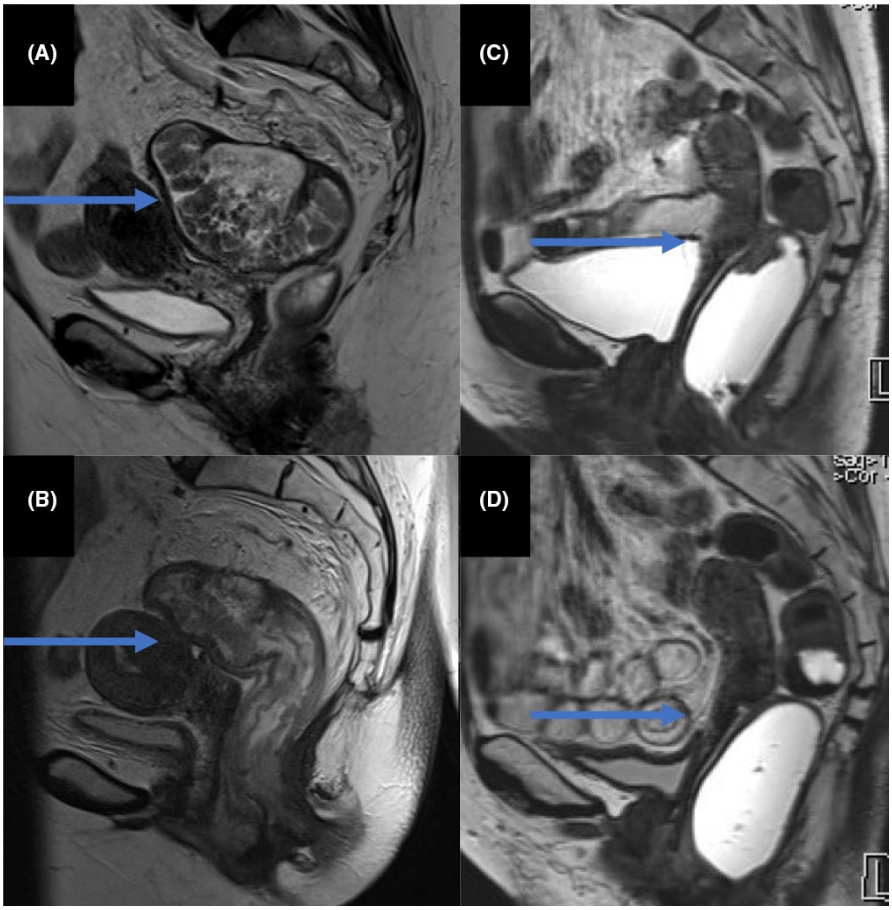

FIGURE 1 Example of response to chemoradiotherapy: sagittal T2-weighted MR images of response to chemoradiotherapy from a patient with a mucinous carcinoma (A), (B) versus a patient with an adenocarcinoma (C), (D). Note the typical mucinous high signal intensity on images (A) and (B) and the difference in response to chemoradiotherapy

Chemoradiotherapy

The CRT scheme was based on the Dutch guidelines. Radiotherapy was administered 5 days per week at a daily dose per fraction of 1.8–2 Gy, up to a total dose of 45–50.4 Gy in 25–28 fractions. Systemic therapy consisted of capecitabine 825–1.000 mg/m^2 twice a day during radiotherapy treatment.

Surgery

The surgical procedure was based on total mesorectal excision principles. Depending on the stage and the location of the tumour, the patient underwent an abdomino-perineal resection, a low anterior resection or a multivisceral excision.

Histopathological examination

The CRM was considered positive when the distance of the CRM to the tumour was ≤1 mm. We defined in the present cohort a CRM of 1 mm compromised by acellular mucin as a clear CRM and a margin invaded by mucin with associated tumour cells as an involved CRM. The resected specimens were classified using the Fifth American Joint Committee on Cancer TNM staging [21]. Patients with a ypT0N0 were defined as pathological complete responders after CRT.

Statistical analysis

Descriptive statistics were expressed as median with standard deviation for continuous variables. Differences between groups were calculated by using the Mann–Whitney *U* test for continuous variables. The Pearson χ^2 test or Fisher's exact tests, if appropriate, were used for categorical variables. In survival analysis, disease-free survival and overall survival were defined as the time from the date of operation to the date of disease recurrence or death, date of censoring or end of follow-up. Patients who were alive at the end of follow-up were censored in the survival analysis. The equality of distributions was compared with log rank testing. Multivariate analysis regarding local recurrence and overall survival was performed using the Cox proportional hazard model. Statistical significance was considered at $P \leq 0.05$. Statistical analyses were performed using SPSS software version 23 (IBM, Armonk, New York, USA).

RESULTS

Between 2002 and 2014, around 700 LARC patients were treated in the two hospitals. In 102 patients, of whom 29 were diagnosed with mucinous carcinoma, a diagnostic and restaging MRI could be retrieved and re-evaluated by the radiologist. Baseline characteristics are shown in Table 1. No differences regarding age, sex, nodal

stage, tumour distance to the anorectal junction and the presence of extramural venous invasion were found. A more advanced tumour stage (58.6% vs. 28.8% cT4 tumours, $P = 0.002$) as well as more frequent involvement of the MRF (96.6% vs. 61.6%, $P < 0.001$) were seen at baseline MRI in mucinous carcinoma versus adenocarcinoma patients. All patients underwent surgery after preoperative CRT.

Response evaluation at restaging MRI after CRT

Patients underwent restaging MRI after completion of CRT, with a median of 10 weeks (range 6–21) after start of preoperative CRT. The results are shown in Table 2. Response evaluation showed significant downstaging to CRT in adenocarcinoma patients ((y)cT stage $P = 0.01$; (y)cN stage $P < 0.001$) while in mucinous carcinoma patients response evaluation showed no significant downstaging to CRT ((y)cT stage $P = 0.89$; (y)cN stage $P = 0.07$). A significant response (>75% tumour size reduction or fibrosis) was seen in 72.6% of adenocarcinoma patients compared to 31.0% of mucinous carcinoma patients ($P < 0.001$). For example, Figure 1 shows the difference in response of mucinous carcinoma versus adenocarcinoma to CRT using T2-weighted MR images pre- and post-CRT. No local tumour growth after CRT was seen in adenocarcinoma patients compared to 17.2% of mucinous carcinoma patients ($P < 0.001$). Furthermore, adenocarcinoma patients demonstrated significantly less involvement of the MRF (61.6% vs. 37.0%, $P = 0.003$) at restaging MRI, compared to no significant differences of MRF involvement pre- versus post-CRT (96.6% vs. 86.2%, $P = 0.16$) in mucinous carcinoma patients. A total of nine adenocarcinoma patients were identified with a ycT0 tumour, of whom seven were classified as a radiological complete response (ycT0N0). No ycT0 or complete response at restaging MRI was seen in the mucinous carcinoma group. Tumour progression after CRT was observed in five patients, all in the mucinous carcinoma group.

Histopathological results

The histopathological results of all patients are shown in Table 3. Mucinous carcinoma patients showed a significantly more advanced ypT stage compared with the adenocarcinoma patients ($P = 0.001$). The proportion of ypT4 tumours was 44.8% in mucinous carcinoma patients versus 8.2% in adenocarcinoma patients. A resection with a clear CRM was achieved significantly less often in mucinous carcinoma patients (72.4% vs. 98.6%; $P < 0.001$).

Of the nine patients who underwent a resection with an involved CRM, eight were diagnosed with a mucinous tumour on baseline MRI. In four mucinous carcinoma patients, an involved CRM was caused due to a mucin pool containing residual tumour cells. Seven out of nine patients were restaged preoperatively with a ycT4 tumour with a threatened MRF on MRI after CRT.

Recurrence and prognosis

Median follow-up after surgical treatment was 37 months (range 3–124) for mucinous carcinoma patients and 54 months (3–141) for adenocarcinoma patients. During follow-up, the cumulative incidence of local recurrence in mucinous carcinoma patients was 27.5% ($n = 8$) versus 6.8% ($n = 5$) in adenocarcinoma patients. In the multivariate regression analysis, mucinous carcinoma was an independent prognostic factor for local recurrence (Table 4) (hazard ratio 3.6; 95% CI 1.1–12.4, $P = 0.04$). No differences were observed regarding overall and disease-free survival during follow-up in multivariate analysis.

DISCUSSION

The study presented is one of the largest cohorts of locally advanced mucinous rectal cancer patients with pre- and post-chemoradiation MRI staging and long-term follow-up. As a primary outcome, mucinous carcinoma demonstrated a significantly worse response after CRT on MRI compared to adenocarcinoma. This also resulted in higher rates of involved CRMs at pathology among the mucinous carcinoma patients. Although the local recurrence rate seemed higher in the mucinous carcinoma group, disease-free and overall survival was not statistically different between the groups on multivariate analyses.

TABLE 1 Baseline characteristics

	Mucinous carcinoma ($n = 29$)	Adenocarcinoma ($n = 73$)	*P* value
Sex (male)	19 (65.5)	46 (63)	0.81
Age (median, range)	61 (37–81)	62 (28–82)	0.19
Tumour distance from anal verge in cm (median, range)	2.4 (0–12.3)	2.2 (0–14.0)	0.85
Surgical procedure			0.07
LAR	11 (37.9)	39 (53.4)	
APR	15 (51.7)	33 (45.2)	
Exenteration	3 (10.3)	1 (1.4)	

Note: Data are *n* (%) if not otherwise specified.

Abbreviations: APR, abdomino-perineal resection; LAR, low anterior resection.

TABLE 2 MRI results: primary staging versus restaging after CRT

	Mucinous carcinoma pre-CRT (*n* = 29)	Mucinous carcinoma post-CRT (*n* = 29)	*P* value†	Adenocarcinoma pre-CRT (*n* = 73)	Adenocarcinoma post-CRT (*n* = 73)	*P* value‡
(y)cT stage			0.89			0.01
T0	0	0		0	9 (12.3)	
T1	0	0		0	0	
T1/2	0	0		0	3 (4.1)	
T2	1 (3.4)	2 (6.9)		13 (17.8)	17 (23.3)	
T3a/b	2 (6.9)	1 (3.4)		24 (32.9)	14 (19.2)	
T3c/d	9 (31.0)	9 (31.0)		15 (20.5)	14 (19.2)	
T4	17 (58.6)	17 (58.6)		21 (28.8)	16 (21.9)	
(y)cN stage			0.07			<0.001
N0	11 (37.9)	18 (62.1)		19 (26.0)	46 (63)	
N+	18 (62.1)	11 (37.9)		54 (74.0)	27 (37.0)	
EMVI positive	10 (34.5)	7 (24.1)	0.39	15 (20.5)	13 (17.8)	0.67
MRF involvement	27 (96.6)	25 (86.2)	0.16	45 (61.6)	27 (37.0)	0.003
Significant response		9 (31.0)			53 (72.6)	
Local tumour growth		5 (17.2)			0	

Note: Data are *n* (%) if not otherwise specified.

Abbreviations: CRT, chemoradiotherapy; EMVI, extramural venous invasion; MRF, mesorectal fascia.

†Mucinous carcinoma pre-CRT versus mucinous carcinoma post-CRT.

‡Adenocarcinoma pre-CRT versus adenocarcinoma post-CRT.

TABLE 3 Pathology results

	Mucinous (*n* = 29)	Adenocarcinoma (*n* = 73)	*P* value
ypT stage			<0.001
T0	3 (10.3)	13 (17.8)	
T1	0 (0)	7 (9.6)	
T2	1 (3.4)	26 (35.6)	
T3	12 (41.4)	21 (28.8)	
T4	13 (44.8)	6 (8.2)	
ypN stage			0.09
N0	17 (58.6)	50 (68.5)	
N1	5 (17.2)	17 (23.3)	
N2	7 (24.1)	6 (8.2)	
Complete response (ypT0N0)	2 (6.9)	9 (14.1)	0.43
Complete resection (R0, CRM–)	21 (72.4)	72 (98.6)	<0.001

Note: Data are *n* (%) if not otherwise specified.

Mucinous rectal cancer is regarded as an unfavourable tumour subtype regarding stage and response to preoperative (chemo)radiotherapy treatment. In the present study, mucinous carcinoma patients were at baseline diagnosed with more advanced tumour stages and higher rates of a threatened MRF on MRI compared to adenocarcinoma patients, in contrast to earlier studies [22,23]. Yu et al. and Shin et al. described the effect of preoperative CRT on histological outcomes of mucinous rectal cancer compared to non-mucinous rectal cancer. The difference, regarding baseline clinical tumour stage, can be explained by the less advanced cT stage of adenocarcinoma included in our group (82.2% cT3-4), compared to the included patients from the work of Yu et al. (96%) and Shin et al. (93.9%). There were no clear differences regarding cN stage (74%) compared with the included patients of Shin et al. (76%).

At restaging MRI after CRT, less downstaging as well as higher rates of MRF involvement were observed in the mucinous carcinoma

TABLE 4 Multivariate Cox regression analysis

	Hazard ratio	95% CI	*P* value
Local recurrence (adenocarcinoma ref)			
Mucinous carcinoma	3.6	1.1–12.4	0.04
ypT	1.6	0.9–2.9	0.14
ypN	1.4	0.7–2.9	0.36
Age	1.0	0.9–1.1	0.15
Overall survival (adenocarcinoma ref)			
Mucinous carcinoma	1.5	0.7–3.3	0.31
ypT	1.5	1.1–2.1	0.02
ypN	1.3	0.8–2.0	0.24
Age	1.0	1.0–1.1	0.31
Disease-free survival (adenocarcinoma ref)			
Mucinous carcinoma	0.8	0.4–1.9	0.67
ypT	1.4	1.0–1.9	0.08
ypN	2.0	1.3–3.0	0.002
Age	1.0	1.0–1.0	0.23

patients compared to the adenocarcinoma patients. A poor response to CRT can influence the probability of an involved CRM, which is one of the key prognostic factors in rectal cancer treatment [24]. An involved MRF was seen at restaging MRI in the vast majority of patients after CRT (86.2%). This resulted in a higher number of involved CRMs in the mucinous carcinoma patients. This reflects the need for specialized tertiary care for locally advanced tumours, as suggested by Hagemans et al. who described the association with improved survival if cT4 tumours were treated in high volume hospitals [25].

Histopathological examination also showed less tumour downstaging in the mucinous carcinoma group with more than 80% of mucinous carcinoma staged as a ypT3 or ypT4 tumour. These results are in line with a cohort of 16 resected mucinous tumours described by Oberholzer et al., where only three out of 16 patients showed T-stage downsizing on histopathology [6]. This has also been described in a recent population-based study, where a mucinous subtype demonstrated a significantly decreased probability (OR 0.57, $P = 0.01$) for pathological complete response to CRT [26].

A high rate of involved CRM (27.6%) was reported in the present study which is comparable with other cohorts of mucinous rectal tumours. In the cohort of Oberholzer et al., 50% of patients had involved margins whereas this was 35% in a cohort of LARC patients from Hugen et al. [5,6]. Even after long-course CRT and surgery in a specialized tertiary referral centre, achieving a clear margin remains a major challenge. Therefore, if a mucinous tumour with an invaded MRF is described in the multidisciplinary team meeting, one might consider referring patients to centres with experience beyond total mesorectal excision surgery [27].

There are patients diagnosed with mucinous carcinoma that demonstrate acellular mucin, free of tumour cells, on histological analysis after CRT and the effects of an involved CRM caused by these acellular mucin pools are a subject for debate. Shia et al. described a cohort of mucinous rectal cancer and provided evidence that mucin pools without associated tumour cells do not have a significant adverse impact on oncological outcome in terms of recurrence and survival [28]. Therefore, we chose in the present cohort to label a CRM of 1 mm compromised by acellular mucin as a clear CRM and a margin invaded by mucin with associated tumour cells as an involved CRM.

The local recurrence rate was significantly increased in the group of mucinous rectal cancer. After multivariate analysis, correcting for pathological tumour and nodal stage, mucinous rectal cancer on pre-treatment MRI remained only significantly associated with local recurrence, without influencing disease-free or overall survival. This is in contrast with the study on LARC by Hugen et al. describing no differences regarding local recurrence during long-term follow-up (15% in mucinous carcinoma patients vs. 10% in non-mucinous patients) [5]. They included LARC patients as well, in the period from 1998 to 2013, from the same two hospitals as in the present study. However, a larger cohort of 58 mucinous carcinoma patients and 482 adenocarcinoma patients with comparable long-term follow-up was reported. In the present study, only patients with LARC who underwent pre- and post-CRT MRI between 2002 and 2014 were included, so some overlap of patients will be present. The main limitation of this study was the limited number of included patients with a mucinous tumour and therefore one must be cautious interpreting the results regarding oncological outcome of the present study. However, locally advanced mucinous rectal cancer remains a rare entity, so larger cohorts or prospective studies will be very challenging. Furthermore, the retrospective design of the present study has its obvious disadvantages in terms of selection bias and follow-up accuracy.

In conclusion, this is the first study describing in detail the worse response of mucinous carcinoma after CRT at restaging MRI, which supports earlier studies that described the poor response of this subtype at pathology. High rates of involved CRMs were seen in the mucinous group, which contributes to the high local recurrence rate during follow-up. No influence on disease-free or overall survival could be demonstrated. Locally advanced mucinous rectal cancer remains a challenging entity in rectal cancer surgery. Further research should focus on achieving a better response to preoperative treatment, in order to improve long-term results.

CONFLICT OF INTEREST

The manuscript has been prepared in accordance with the style of the journal, and all authors have approved its contents. This manuscript is not being considered for publication elsewhere and the findings of the manuscript have not been previously published. There is no conflict of interest.

AUTHOR CONTRIBUTIONS

Study concepts: TK, RS, NH, HdW, HR; Study design: TK, RS, NH, HdW, HR; Data acquisition: TK, RS, NH, SvK, JvdH, Quality control

of data and algorithms: TK, RS; Data analysis and interpretation: TK, RS, NH, HdW, HR; Statistical analysis: TK, RS, NH; Manuscript preparation: TK, RS, NH, HdW; Manuscript editing: TK, RS, NH, SvK, JvdH, JN, IN, PvZ MV, HR, HdW, PvZ; Manuscript review: TK, RS, NH, SvK, JvdH, JN, IN, PvZ, MV, HR, HdW, PvZ.

ETHICAL APPROVAL

Ethical approval for this study was waived by the local medical ethics committee.

DATA AVAILABILITY STATEMENT

Data are available on request due to privacy/ethical restrictions.

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