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ORIGINAL ARTICLE

Pretreatment identification of patients likely to have pathologic complete response after neoadjuvant chemoradiotherapy for rectal cancer

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Abstract

Purpose In selected patients, a wait-and-see strategy after chemoradiotherapy for rectal cancer might be feasible provided that the probability of pathologic complete response (pCR) is high. This study aimed to identify clinical parameters associated with pCR. Furthermore, we attempted to identify subgroups with increased probability of pCR that might aid in clinical decision making.

Methods A total of 6444 patients that underwent surgical resection of a single primary carcinoma of the rectum after neoadjuvant chemoradiotherapy (nCRT) between January 2009 and December 2016 in the Netherlands were included in the study. Data on the outcome variable, pCR, and potential covariates were retrieved from a nationwide database. The variables included in the analysis were selected based on previous studies and were analyzed using univariate and multivariate logistic regression analyses.

Results pCR was observed in 1010 patients (15.7%). Pretreatment clinical tumor stage and signs of obstruction were independently associated with pCR. Nodal stage and presence of metastatic disease decreased chances of pCR significantly. The best response rate was observed in patients diagnosed with a non-obstructive, well-/moderately differentiated adenocarcinoma of the lower rectum with no clinical apparent nodal or distant metastatic disease (pCR ratio 18.8%). The percentage of patients demonstrating pCR decreased in case of symptoms of pretreatment obstruction or poorly differentiated tumors (pCR ratio of 11.8 and 6.7%, respectively).

Conclusion This nationwide study confirms several of the previously reported clinical predictors of pCR.

Keywords Colorectal · Complete response · Neoadjuvant chemoradiotherapy · Rectal cancer

Introduction

Neoadjuvant chemoradiotherapy (nCRT) preceding surgery for locally advanced rectal carcinoma has beneficiary effects on local control [1–3]. Current conventional fractionation nCRT protocols have demonstrated pathologic complete response (pCR) rates ranging between 14 and 25% [1, 3, 4]. In turn, pCR has been associated with fewer local recurrences and an improved 5-year survival [5]. In the past decade, several studies have described the results of patients estimated to have complete clinical response on imaging and proctoscopy after nCRT that were not treated with surgery [6, 7]. In selected patients, careful follow-up through endoscopic, clinical, and radiographic evaluation demonstrated low rates of local recurrence and distant manifestation of disease [5–8]. In addition to a watch-and-wait approach, low local recurrence rates after local excision alone, in patients estimated to have complete clinical response, have been reported [9–12]. In order to select patients that might benefit from these rectal-preserving strategies, an accurate estimation should be made whether an individual patient is likely to have pCR.

Unfortunately, clinical estimation of complete response is not an accurate predictor of pCR. Digital rectal examination,

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proctoscopy, or examination under anesthesia does not accurately predict tumor response [13]. Several studies have investigated the role of imaging modalities such as transrectal endoscopic ultrasound, magnetic resonance imaging, and integrated positron emission tomography. None of these modalities have proven to accurately diagnose pCR [14–17]. Some promising results have been shown for diffusion-weighted MRI [18]. In addition to information on tumor size, diffusion-weighted MRI provides information on tumor function and biology. Despite this, differentiating between areas of fibrosis and tumor remains difficult, resulting in frequent overestimation of residual tumor [19]. Thus, the best estimation of true complete response remains the full pathologic examination of the resected specimen.

As outlined above, in selected patients, a conservative treatment strategy after chemoradiotherapy might be feasible provided that the risk on local recurrence is low and recurrent disease is detected at an early stage [4]. Despite modern imaging technology, selecting patients likely to have pCR after nCRT remains difficult leading to frequent overestimation of residual tumor. Several studies have described potential predictors for pCR after nCRT. However, most studies address a limited number of parameters in a relatively small and selected population. The aim of this study was to confirm and quantify the association between pCR and several previously identified clinical predictors. Based on the variables that were found to be independently associated with pCR, an attempt was made to identify subgroups with high or low probability on pCR. Since previous studies are based on relatively small and selected patient populations, we chose to investigate a relatively large number of parameters in an unselected nationwide population.

Materials and methods

Population

Data were obtained from the Dutch ColoRectal Audit (DCRA, www.dica.nl/dcra) database. In this database, data are recorded on all patients that have undergone colorectal cancer surgery in the Netherlands. Because participation in the DCRA is made obligatory by the Dutch Health Care Inspectorate, all 92 hospitals performing colorectal cancer surgery in the Netherlands participate in data delivery to this nationwide database. In the DCRA, data are recorded considering 212 parameters including demographic characteristics, pre-operative work-up, pre-operative clinical staging, procedures performed, and results of pathological examination. Between January 2009 and December 2016, a total of 6520 patients were recorded to have undergone surgical resection of a single primary carcinoma of the rectum after nCRT in the DCRA database. Patients without information on postoperative tumor staging or date of surgery were excluded from the analysis. A total number of 6444 patients met the minimal data requirements and were found eligible for analysis. In case of a relatively large amount of missing data (> 5%) or data missing not at random (MNAR) on a certain parameter, this parameter was not included in the main multivariate analysis. These variables were analyzed using univariate analysis only and reported separately. A schematic representation of the inclusion process is displayed in Fig. 1. As this was an observational study, and study data could not be traced back to individual patients, the study received ethical review board exemption status.

Definitions

The primary outcome variable was pCR which was defined as the absence of histological evidence of vital tumor cells at the primary tumor site or locoregional lymph nodes in the resected specimen. Mortality was defined as mortality of any cause, in the course of the concerning hospital admission or within 30 days after surgery. Parameters that were considered to be potentially associated with the primary outcome variable pCR were selected based on the results of previously published studies. Variables considered were; distance from the anal verge [20, 21] in centimeters measured by the endoscopist, tumor size (pretreatment clinical T stage) [22], nodal involvement (pretreatment clinical N stage) [22], metastatic disease (pretreatment clinical M stage), diabetes mellitus [23, 24] (stratified for insulin-dependent and non-insulin dependent diabetes mellitus), histologic subtype (defined as adeno-, mucinous carcinoma), time interval from nCRT to surgery [21, 25], and pre-operative anemia [21] (defined as pre-operative hemoglobin levels < 7 mmol/l in male patients and hemoglobin levels < 6.5 mmol/l in female patients). In case no data were entered in the database with regard to the presence of anemia, it was assumed to be absent. Pretreatment clinical and posttreatment pathological tumor and nodal classification was done according to the sixth edition of the American Joint Committee on Cancer TNM classification system.

Other covariates that were included in the analysis were age at time of diagnosis, year of surgery, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, pretreatment distance to mesorectal fascia (MRF) (defined as < 1 mm on MRI), vascular or lymphatic invasion, and signs of pretreatment obstruction (in case no data were entered in the database with regard to the presence of sigs of obstruction, it was assumed to be absent).

Power analysis

Twelve covariates were investigated. Based on a rule of thumb of 10 cases per parameter [26], we estimated to require 120

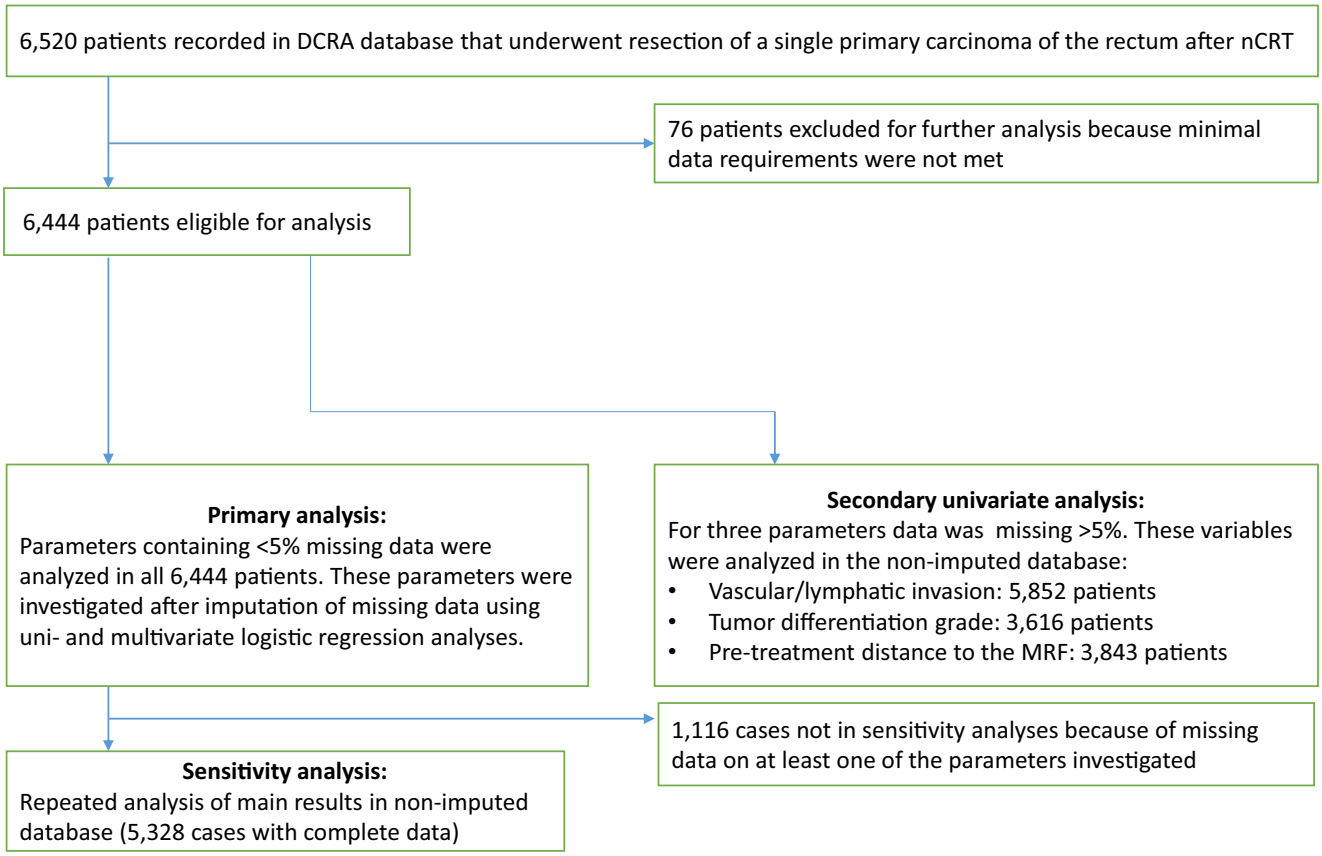

Fig. 1 Patient inclusion

cases of pCR in our study population. Previous reports from the DCRA database demonstrated that 22% of patients had either AJCC stage III or IV disease. According to current nationwide guidelines (http://www.oncoline.nl/colorectaalcarcinoom), all patients with stage IV disease and a large part of patients with AJCC stage IIIa and IIIb disease should be considered for nCR. Based on an estimated 10% pCR rate, obtaining a population with at least 120 cases of pCR from the DCRA database seemed procurable.

Handling of missing data

Missing value analysis was conducted by performing Little's MCAR test in order to identify potential patterns in missing data that might bias the analysis. In case of a not significant Little's MCAR test, data were considered to be missing completely at random (MCAR) and therefore found to be eligible for multiple imputation. As a second prerequisite for data imputation, variables were only considered for the imputation technique when the amount of missing of data was smaller than 5%. Seven parameters met the two abovementioned criteria: BMI (4.2% missing data), distance from the anal verge (3.7% missing data), ASA classification (0.5% missing data), pretreatment clinical T stage (1.8% missing data), pretreatment clinical N stage (2.6% missing data), pretreatment clinical M stage (2.6% missing data), and histologic subtype (2.3% missing data). For these variables, Little's MCAR test was not significant (chi-square = 0.862, DF = 2, Sig. = 0.650). For these parameters, the data were concluded to be MCAR and therefore multiple missing value imputation technique was considered safe and was applied.

Statistical analysis

Patient and disease characteristics were investigated and reported. Univariate logistic regression analyses were performed to identify variables associated with the primary outcome variable: pCR. Continuous variables were categorized into clinical relevant subgroups. This way, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. After univariate analysis, multiple logistic regression analyses were performed to identify variables that were independently associated with pCR. Parameters with a P value under 0.250 in univariate analysis were entered in the model using a backward stepwise approach [27]. The robustness of our findings was tested by conducting a sensitivity analysis. This was done by repeating the analysis of our main results on the non-imputed database using only complete cases (cases containing no missing data on the concerning parameters). Three variables did not meet the criteria for data imputation: vascular or

lymphatic invasion (9.2% missing data), tumor differentiation grade (43.9% missing data), and pretreatment distance to the MRF (40.4% missing data). In a secondary analysis, these variables were analyzed using univariate analysis only. For this analysis, the original, non-imputed database was used. Based on the potential risk estimators that were identified and quantified, we attempted to identify subgroups with either high or low risk on pCR. *P* values under 0.05 were considered to be statistically significant. All calculations were performed using the Statistical Package for the Social Sciences (SPSS) version 23 (Chicago, IL, USA).

Results

A total of 6444 patients met the inclusion criteria and were selected from the DCRA database. The patient characteristics of this population are summarized in Table 1. Median age was 65 years (range 18–93). All patients were operated on electively for a primary malignancy of the rectum. In most cases, the tumor was an adenocarcinoma (90.6%). Procedures performed consisted mostly of either an anterior resection (56.5%) or an abdominoperineal resection (40.8%). In a small percentage of cases (0.7%), the exact procedure was not specified. After a large majority of procedures were performed, no cancerous cells were seen in the circumferential resection margins of the resected specimen (5967, 92.6%).

The presence of our primary outcome variable, pCR, was observed in 1010 patients (15.7%). During the study period, the percentage of patients observed to have pCR increased

Table 1 Patient and disease characteristics

	Number of patients $N = 6444$	%
Gender		
Male	4.113	63.8
Female	2.331	36.2
Age		
< 50	563	8.7
50–60	1359	21.1
60–70	2486	38.6
70–80	1771	27.5
> 80	263	4.1
ASA classification		
1	1742	27.0
2	3928	61.0
3	724	11.2
4	19	0.3
Missing data	31	0.0
Diabetes mellitus		
No	5663	87.9
Yes	781	12.1
Pre-operative anemia		
No	5683	88.2
Yes	761	11.8
BMI		
< 20	351	5.4
20–25	2354	36.5
25–35	3267	50.7
> 35	200	3.1
Missing data	272	4.2
Pre-operative signs of obstruction		
No	6162	95.6
Yes	282	4.4
Distance to the anal verge (cm)		
Low (0–6)	3424	53.1
Mid (7–11)	2033	31.5
High (≥ 12)	750	11.6
Missing	237	3.7
Clinical T stage		
cT1	44	0.7
cT2	494	7.7
cT3	4443	68.9
cT4	1208	18.7
Missing data	255	3.9
Clinical N stage		
cN0	1104	17.1
cN1	2262	35.1
cN2	2646	41.1
Missing data	169	2.6
Clinical M stage		
M0	5371	83.3
M1	467	7.2
Missing data	168	2.6
Year of surgery		
2009–2010	1114	17.3
2011–2012	1810	28.1
2013–2014	1943	30.2
2015–2016	1577	24.5
Procedure		
Anterior resection	3640	56.5
Abdominoperineal resection	2627	40.8
Missing data/not specified	177	2.7
Histologic subtype		
Adenocarcinoma	5840	90.6
Mucinous carcinoma	287	4.5
Other/non-specified	166	4.9

ASA American Society of Anesthesiologists, *BMI* body mass index

gradually from 13.5% in 2009 and 2010 up to 16.8% in 2015 and 2016. Partial response (downgrading of TNM stage) was observed in 3837 patients (59.5%). Reported mortality was 1.2% ($n = 75$). During the study period, the number of patients treated with nCRT and subsequent surgery for rectal carcinoma increased over the years (17.3% of the included patients were treated in 2009 and 2010 compared to 24.5% of the included patients treated in 2015 and 2016).

Analysis *excluding* vascular or lymphatic invasion, tumor differentiation grade, and pretreatment distance to the MRF

Parameters that were associated with pCR in univariate analysis were pre-operative anemia (presence of anemia increased the probability of pCR: OR 1.35; 95% CI 1.11–1.64), pretreatment signs of obstruction (signs of obstruction decreased the probability of pCR: OR 0.53; 95% CI 0.36–0.81), pretreatment clinical M stage (patients with metastatic disease demonstrated a decreased probability for pCR: OR 0.35; 95% CI 0.24–0.50), and histologic subtype (patients with a mucinous carcinoma demonstrated a decreased probability for pCR compared to adenocarcinoma: OR 0.56; 95% CI 0.36–0.85). Table 2 summarizes the unadjusted odds ratios of the variables that were tested.

Table 2 Results of univariate analysis (=6444)

Parameter	OR (95% CI)		*P* value
ASA classification			0.10
1		1	
2	0.90	(0.78–1.05)	0.19
3	0.73	(0.57–0.94)	0.02
4	0.60	(0.15–2.46)	0.46
Diabetes mellitus			0.29
No		1	
NIDDM	1.02	(0.81–1.29)	0.86
IDDM	0.71	(0.46–1.11)	0.14
Pre-operative anemia			
No		1	
Yes	1.35	(1.11–1.64)	0.002
Pretreatment signs of obstruction			
No		1	
Yes	0.53	(0.36–0.81)	0.003
Distance to the anal verge (cm)			0.13
Low (0–6)		1	
Mid (7–11)	0.90	(0.78–1.05)	0.17
High (≥ 12)	0.82	(0.66–1.03)	0.08
Clinical T stage			0.15
cT1		1	
cT2	0.78	(0.39–1.55)	0.48
cT3	0.71	(0.37–1.36)	0.30
cT4	0.45	(0.23–0.88)	0.02
Clinical N stage			0.05
cN0		1	
cN1	1.08	(0.88–1.32)	0.31
cN2	0.90	(0.74–1.09)	0.20
Clinical M stage			0.000
M0		1	
M1	0.35	(0.24–0.50)	0.000
Year surgery			0.08
2009–2010		1	
2011–2012	1.16	(0.94–1.44)	0.17
2013–2014	1.30	(1.05–1.60)	0.02
2015–2016	1.25	(1.01–1.56)	0.04
Procedure			
Anterior resection		1	
Abdominoperineal resection	1.08	(0.94–1.24)	0.27
Histologic subtype			
Adenocarcinoma		1	
Mucinous carcinoma	0.56	(0.36–0.85)	0.006
Interval nCRT to surgery (weeks)			0.12
1–8		1	
9–16	2.18	(0.67–7.12)	0.19
17–24	2.26	(0.71–7.18)	0.16
> 24	2.07	(0.64–6.68)	0.22

OR odds ratio, *CI* confidence interval, *ASA* American Society of Anesthesiologists

Variables that were not significant in univariate analysis but were eligible (overall P value < 0.25) for multivariate analysis were pretreatment clinical N stage (patients pre-operatively staged as N2 demonstrated a decreased probability for pCR compared to patients staged N0 and N1: OR 0.90; 95% CI 0.74–1.09), distance to the anal verge (closer proximity to the anal verge was associated with higher probability of pCR), year of surgery (during the study period the probability of pCR increased gradually), ASA classification (higher ASA classification was associated with decreased probability of pCR), clinical T stage and interval nCRT to surgery (an increased time interval from nCRT to surgery was associated with a higher pCR ratio). A total number of 11 parameters were thus found eligible for multivariate analysis. The results of the multivariate analysis are demonstrated in Table 3. Variables independently associated with pCR were pre-operative anemia (anemic patients were more likely to have pCR: OR 1.28; 95% CI 1.04–1.57), pretreatment signs of obstruction (patients with signs of obstruction were less likely to have pCR: OR 0.61; 95% CI 0.40–0.94), clinical M stage (patients with metastatic disease were less likely to have pCR: OR 0.35; 95% CI 0.24–0.52), year of surgery

Table 3 Results of multivariate analysis (n = 6444)

Parameter	OR (95% CI)		*P* value
Pre-operative anemia			
No		1	
Yes	1.28	(1.04–1.57)	0.019
Pretreatment signs of obstruction			
No		1	
Yes	0.61	(0.40–0.94)	0.024
Clinical T stage			0.23
cT1		1	
cT2	0.79	(0.36–1.71)	0.54
cT3	0.73	(0.35–1.54)	0.41
cT4	0.54	(0.25–1.16)	0.11
Clinical N stage			0.28
cN0		1	
cN1	0.91	(0.74–1.13)	0.39
cN2	0.77	(0.48–1.23)	0.27
Clinical M stage			
M0		1	
M1	0.35	(0.24–0.52)	0.00
Year of surgery			
2009–2010		1	
2011–2012	1.21	(0.96–1.52)	0.12
2013–2014	1.39	(1.11–1.75)	0.01
2015–2016	1.46	(1.15–1.85)	0.00
Histologic subtype			
Adenocarcinoma		1	
Mucinous carcinoma	0.57	(0.38–0.88)	0.01

OR odds ratio, *CI* confidence interval

(2009–2010 versus 2015–2016: OR 1.46; 95% CI 1.15–1.85), and histologic subtype (patients with a mucinous carcinoma demonstrated a decreased probability for pCR compared to adenocarcinoma: OR 0.57; 95% CI 0.38–0.88). Tumor and nodal stages were included in the logistic regression model. However, the overall *P* values of the corresponding regression coefficients did not prove to be significant in the multivariate analysis.

Sensitivity analysis Repeating multivariate analysis in the non-imputed database using exclusively cases with complete data (5328 cases, 82.7%) yielded comparable results.

Univariate analysis of vascular or lymphatic invasion, tumor differentiation grade, and pretreatment distance to the MRF

Table 4 summarizes the unadjusted odds ratios of the variables that were tested in this way. Vascular or lymphatic invasion was associated with pCR (presence of invasiveness decreased probability of pCR: OR 0.15; 95% CI 0.10–0.23). Tumor differentiation was also found to be associated with pCR (poorly differentiated tumors demonstrated decreased probability of pCR: OR 0.44; 95% CI 0.24–0.79). In contrast to these parameters, pretreatment distance to the MRF could not be associated with pCR (OR 1.06; 95% CI 0.89–1.27).

Table 4 Results of univariate analysis on complete cases of variables MNAR/large amount of missing data

Parameter	OR (95% CI)		*P* value
Vascular/lymphatic invasion			
No		1	
Yes	0.15	(0.10–0.23)	0.00
Tumor differentiation grade			
Well/moderate		1	
Poor	0.44	(0.24–0.79)	0.01
Distance to MRF			
≥ 1 mm on MRI		1	
< 1 mm on MRI	1.06	(0.89–1.27)	0.90

MNAR missing not at random, *OR* odds ratio, *CI* confidence interval, *MRF* mesorectal fascia

Subgroups with either high or low risk on pCR

An improved response rate was observed in a subgroup of 444 patients (6.8%) diagnosed with a non-obstructive well-/moderately differentiated adenocarcinoma of the lower rectum with no clinical apparent nodal or distant metastatic disease (84 patients with pCR, 18.9%). The percentage of patients demonstrating pathologic complete response increased when surgical treatment was performed between 16 and 24 weeks post nCRT (33 out of 149 patients with pCR, ratio 22%). In the subgroup of patients with a non-obstructive well-/moderately differentiated adenocarcinoma ($n = 5675$, 88.1%), the presence of nodal involvement had little effect on pCR ratio while the presence of distant metastatic disease or poor tumor differentiation grade drastically decreased pCR ratio (pCR ratio of 8.3 and 6.7%, respectively; decrease 10.5 and 12.1%, respectively).

The lowest pCR rates were observed in patients with relatively large tumors. Patients with a non-obstructive tumor large (T4) adenocarcinoma demonstrated an overall response ratio of 11.4% (115 out of 1012 patients). This ratio decreased to 7.9% in the case of pretreatment symptoms/signs of obstruction (8 patients with pCR out of 110). Patients with tumor stage 4 adenocarcinoma without signs of obstruction appeared to do worse in the case of nodal involvement (pCR ratio in T4N2M0 patients, 8.7%). Adding the presence of distant metastatic disease worsened the pCR ratio further to 5.1% (4 patients with pCR out of 78). The lowest pCR ratio was observed for patients with large, poorly differentiated tumors (T4N2M0/1 poorly differentiated, pCR ratio 2.4%).

Discussion

In the present study, the association between a set of parameters and pCR after nCRT for rectal cancer was investigated in a nationwide unselected cohort. Variables that were being analyzed were selected, based on previously published smaller cohort studies. In accordance with these studies, we confirmed that a larger tumor size is associated with a decreased pCR rate. Both, pretreatment clinical tumor stage and signs of obstruction (as a proxy for tumor size) were found to be associated with pCR (Tables 2 and 3). Apart from pretreatment tumor stage, nodal stage (especially patients who were pretreatment staged as having at least four positive nodes) and presence of metastatic disease decreased chances of pCR significantly. Furthermore, pCR was confirmed to be related to histologic subtype (in favor of adenocarcinoma), distance to the anal verge, ASA classification (in favor of the lower ASA subgroups), and year of surgery (patients treated at the end of the study period demonstrated higher probability of pCR). There were no significant differences in age, gender, BMI, diabetes mellitus, distance to the MRF on MRI (< 1 mm), and type of procedure performed.

The overall pCR rate was 15.7%. Despite the potential predictors that were confirmed and identified, we were not able to define subgroups with a probability on pCR higher than 21%. The high- and low-risk groups that were identified consisted of relatively small proportions of the study population. For these reasons, accurate prediction of pCR solely based on the pretreatment clinical parameters appeared to be difficult and insufficient to guide clinical decision making. Unfortunately, the concerning surgical procedures for rectal cancer (anterior and abdominoperineal resections) are associated with significant morbidity and mortality. In some subpopulations, procedure-related risks are higher. For example, older age has been associated with a higher 1-year overall, cancer-specific, and cardiovascular-specific mortality [28]. Furthermore, older frail patients are at increased risk of postoperative complications and mortality [29]. Especially in this group of frail elderly patients exposed to increased risks on procedure-related complications, a careful consideration should be made between potential harm and benefit of the treatment options. In order to make a well-balanced treatment decision for these patients, knowledge and consideration of predictors for pCR appear valuable.

As mentioned before, one of the variables associated with pCR was the year of surgery. Over the past 8 years, response rates gradually improved. Interestingly, during the study period (in the year 2014), a new nationwide guideline for the treatment of colorectal carcinoma was introduced in the Netherlands (http://www.oncoline.nl/colorectaalcarcinoom). In this new guideline, the criteria for pretreatment nodal status determination on MRI were adjusted. This was done in order to decrease the false-positive rate of nodal staging on MRI. Furthermore, in the new guideline, criteria for nCRT were specified more clearly compared to the previous guideline. These two changes might have led to a change in patient selection for nCRT which in turn might have led to higher pCR rates over the past years. Apart from tumor size and nodal status, one of the criteria for nCRT that was added in the 2014 Dutch guideline is distance to the MRF smaller than 1 mm on MRI. Unfortunately, this parameter was poorly documented in the database (40.4% missing data), and its impact on pCR rate could therefore not be assessed reliably. However, our results suggest that a distance to MRF smaller than 1 mm on MRI does not influence the probability on pCR. We did not investigate the relation between distance to MRF on MRI and achieving a resection with tumor-free margins. Therefore, we are unable to make any recommendations with regard to its current incorporation as criteria for nCRT in the guideline.

Most parameters that were associated with pCR in our study were also linked to pCR in other studies: tumor size (pretreatment tumor and nodal stage) [22, 30, 31], distance to the anal verge [20, 21], histologic subtype, and interval to surgery [21, 25]. It seems logical that increased tumor size and poor differentiation grade are related with a decreased probability on pCR. Time interval to surgery seems a somewhat less obvious predictor of pCR. It has been postulated that increasing the interval to surgery allows for ongoing tumor necrosis and therefore improves the pCR rate [32]. Previously published studies reported favorable results of using time intervals over 7–8 weeks [22, 32, 33]. Based on these results, we stratified our time intervals and demonstrated a similar result; the odds ratio on pCR was above 2 for all intervals at least 8 weeks post nCRT. These intervals could not be made significant in the multivariate analysis. However, in combination with previously published studies, it seems likely that allowing an interval to surgery of at least 7 to 8 weeks increases the pCR rate.

Like previously reported in other studies, tumors located more closely to the anal verge [20, 21] were more likely to show pCR. Although also reported in other studies, this relation was found to be relatively small (Table 2) and was not significant in the multivariate analysis. In contrast to this finding, other studies have reported no differences in pCR rates related to location [34] or even a higher risk of local recurrence for lower tumors [35]. Altogether, the potential beneficiary effects of tumor location appear to be small and therefore seem to be of little importance as a predictor for pCR. The presence of distant metastatic disease was also considered in our study as a potential predictor of pCR. Like with tumor size, the presence of metastatic disease can be interpreted as an indicator of the aggressiveness of the tumor. We therefore find it not surprising that pCR was strongly related to M stage in the multivariate analysis.

Armstrong et al. demonstrated higher hemoglobin levels in patients with pCR in univariate analysis [21]. This relation

could not be confirmed in their multivariate analysis. Also, a relation between pretreatment anemia and longer term local control has been demonstrated [36]. It has been postulated that anemia contributes to intratumoral hypoxia and tumor resistance to ionizing radiation. However, evidence for this theory is sparse. The relation between anemia and pCR demonstrated in our study seems counterintuitive to this theory and previously published results. In this study, a small effect in favor of anemia was detected (OR 1.28) with a confidence interval approaching 1 (95% CI 1.04–1.57). We cannot offer a molecular-based hypothesis that explains this finding. The relation that was demonstrated could consist of a false-positive one. Another option, more in line with previously published studies, is that if there is a relation, it is a small one (or none). This seems more likely since our study appears to confirm most of the previously demonstrated predictors and consists of a large unselected population of patients in which data were prospectively collected.

The present study has a few limitations that should be mentioned. Firstly, although the database that was used consisted of a large amount of unselected nationwide data, it was primarily designed for benchmark purposes. Although many of the previously described predictors were present in the database, some were poorly documented. Secondly, even though many parameters were documented, several parameters that were previously shown to be predictors of pCR were not present in our database and could therefore not be analyzed (CEA level, the exact nCRT regimen, statin use). Thirdly, it is likely that because of errors during data entry, information bias was created. However, we find it unlikely that wrongness of data was related to the outcome variable pCR. Since our database is large, we expect that this phenomenon has had little influence on our results.

In conclusion, this large nationwide prospective study on predictors of pCR after nCRT for primary carcinoma of the rectum confirms several of the previously reported predictors of pCR. The best response rate was observed in patients diagnosed with a non-obstructive well-/moderately differentiated adenocarcinoma of the lower rectum with no clinical apparent nodal or distant metastatic disease. The worst pCR ratio was observed for patients with large poorly differentiated tumors.

Acknowledgments The presented study was preregistered with the DCRA (https://www.dica.nl/dcra/onderzoek).

Author contributions GB and FS conceived of the study and its design. Statistical analysis was carried out by FS. All authors contributed in drafting the article and revising it critically for intellectual content. All authors read and approved the final manuscript.

Compliance with ethical standards

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

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