A preoperative prediction model for anastomotic leakage after rectal cancer resection based on 13.175 patients

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ABSTRACT

Introduction: This study aims to develop a robust preoperative prediction model for anastomotic leakage (AL) after surgical resection for rectal cancer, based on established risk factors and with the power of a large prospective nation-wide population-based study cohort.
Materials and methods: A development cohort was formed by using the DCRA (Dutch ColoRectal Audit), a mandatory population-based repository of all patients who undergo colorectal cancer resection in the Netherlands. Patients aged 18 years or older were included who underwent surgical resection for rectal cancer with primary anastomosis (with or without deviating ileostomy) between 2011 and 2019. Anastomotic leakage was defined as clinically relevant leakage requiring reintervention. Multivariable logistic regression was used to build a prediction model and cross-validation was used to validate the model.
Results: A total of 13.175 patients were included for analysis. AL was diagnosed in 1319 patients (10%). A deviating stoma was constructed in 6853 patients (52%). The following variables were identified as significant risk factors and included in the prediction model: gender, age, BMI, ASA classification, neo-adjuvant (chemo)radiotherapy, cT stage, distance of the tumor from anal verge, and deviating ileostomy. The model had a concordance-index of 0.664, which remained 0.658 after cross-validation. In addition, a nomogram was developed.
Conclusion: The present study generated a discriminative prediction model based on preoperatively available variables. The proposed score can be used for patient counselling and risk-stratification before undergoing rectal resection for cancer.

1. Introduction

Anastomotic leakage (AL) is one of the most complex problems after restorative rectal cancer surgery leading to reoperations, readmission, increased length of hospital stay, a higher risk for postoperative mortality and worse oncologic outcomes [1–6]. Despite many preventive efforts, it remains a major problem with a reported prevalence between 1 and 19% [4,7–9]. Risk factors have extensively been analyzed and include male gender, height of the anastomosis, ASA score, diabetes, obesity, smoking, malnutrition, corticosteroid use, and neo-adjuvant (chemo)radiotherapy [4,8,10–13].

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Patients discussing an operation for rectal cancer with their physician face the difficult surgical decision whether to have a colorectal/coloanal anastomosis or a permanent colostomy. Most patients consider the idea of a colostomy unfavorable and desire an anastomosis. On the other hand, some patients find that restorative rectal surgery is associated with significantly impaired bowel function, and, moreover, wish to avoid the risk of AL. Such patient preferences should play a major role to improve the quality of shared decision-making. Nevertheless, tools that allow patients to adequately understand the benefits, risks, and potential harms of both treatment methods are scarce and mostly insufficient [14]. A recent study developed and validated a nomogram to predict bowel dysfunction following restorative rectal cancer resection [15]. Available prediction models for AL however are based on small number of patients or lack sufficient discriminative power to be used in clinical practice [16–18].

This study aims to develop a preoperative prediction model, designed to be used during shared-decision making, for anastomotic leakage after rectal cancer resection. To ensure validity, the design uses variables that are established risk factors in literature and the power of a large nation-wide cohort.

2. Methods

A development cohort was formed by using the DCRA (Dutch ColoRectal Audit), a mandatory population-based repository of all patients who undergo colorectal cancer resection in the Netherlands. The database includes patient-level data regarding preoperative clinical staging, co-morbidities, operative details, as well as postoperative course and definitive pathological result. For the present study, no ethical approval or informed consent was required under Dutch law. Details regarding collection and methodology of the DCRA dataset have been published previously [19].The TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) statement is followed to report multivariable prediction model development and validation [20].

2.1. Study population

Data was assembled of patients operated between January 1, 2011 and December 31, 2019. Patients aged 18 years or older were included who underwent an elective rectal resection for cancer with primary anastomosis (with or without deviating stoma) and curative intention. The more recent 'sigmoid take-off' definition for rectal carcinoma was not available in this historical dataset. Therefore, the carcinoma had to be located within 150 mm of the anal verge to be defined as rectal carcinoma, similar to clinical trials [21]. Patients who underwent a successful procedure to treat obstruction (by stoma or stent) prior to an elective rectal resection were included. Excluded were patients who underwent acute resection for obstructive cancer because this group entails a different treatment setting (i.e. inevitable higher risk of AL) [22]. Patients who underwent intra-operative radiotherapy or rectal resection as part of cytoreductive surgery and hyperthermic intraoperative chemotherapy for peritoneal metastases (HIPEC) were also excluded.

2.2. Study outcomes

The outcome of the study is anastomotic leakage within 30 days, defined as the need for endoscopic, percutaneous or operative re-intervention due to the leakage [23].Within the DCRA database, anastomotic leakage was recorded up to 30 days until the year 2018, afterwards 90 days follow-up was applied [24].

2.3. Predictor variables

Candidate predictor variables were identified by reviewing literature and these variables required to be applicable to the pre-operative setting. Variables entered in the model were: age [4], sex [4,8,12,25], BMI [25,26], American Society of Anaesthesiologists (ASA) physical status classification [4,8,25], diabetes [4], lung disease [11], ileo- or colostomy [27], tumor invasion on imaging (clinical T-stage according to TNM) [8,25], tumor height from anal verge as assessed by treating radiologist on pre-treatment sagittal MRI and verified during local multidisciplinary team meeting [8,12,25], neo-adjuvant therapy [8,12,25], and approach (transabdominal (open), transabdominal (scopic), transanal local open, TAMIS, transanal and transabdominal, robot) [4,28].

2.4. Statistical analyses

Summary statistics were provided as whole numbers and percentages for categorical variables, and medians with interquartile range (IQR) for continuous variables. The distribution of categorical variables was tested using the χ^2 test. The distribution of continuous variables was tested using the Mann-Whitney *U* test. Logistic regression analyses were utilized to determine correlation between the primary outcome and predictor variables. Results from the models were reported as odds ratios (OR) and their corresponding 95% confidence intervals (CI). Continuous predictors were transformed using restricted cubic splines if this improved the model fit. Multiple imputation was used to correct for missing data in the multivariable analysis. Backwards selection based on a $p < 0.05$ was used to select predictors in the final model from the previously described predictor variables. Linear predictors from the final model were used to construct a point-based score and nomogram for clinical application. Cross-validation using 10 random samples was used to validate the model. Model performance was evaluated using Harrel's C-index, the Brier score, and a calibration plot of the apparent and cross-validated model. The concordance index (C-index) was used to quantify discriminative value, which is comparable to the area under the receiver operating characteristic (ROC) curve [29]. The Brier score is used to measure the difference between observed and predicted survival per stage, 0 signifies total accuracy, whereas a score of 0.250 indicates no prognostic value. The model was validated on patients operated before- and after 2018 to identify whether difference in follow-up time (30 days vs 90 days) affected discriminative value. All analyses were performed using the *rms*, *TableOne*, and *mice* packages for R 4.0.5 (https://cran.r-project.org/). All tests were 2-sided and $p < 0.05$ defined statistical significance.

3. Results

3.1. Study population

A total of 92.392 patients who underwent colorectal surgery for cancer in the Netherlands were included in the database between 2011 and 2019. After exclusion of patients undergoing colonic surgery (n = 66.055) a total of 26.337 patients remained eligible. Patients were excluded because either emergency surgery was performed (n = 114), intraoperative chemo/radiotherapy was applied (n = 120) or no primary colorectal or coloanal anastomosis was constructed (12.928). Eventually, a total of 13.175 were included for analyses.

3.2. Baseline and perioperative characteristics

Among the patients who were included for analyses, the median age was 66 (IQR 59–72) with a majority of patients being male (n = 8225, (62%)). 7551 (58%) patients received neoadjuvant radio(-chemo)therapy, a laparoscopic approach was performed in 9528 (73%), and a deviating stoma was constructed in 6853 patients (52%). Baseline and perioperative characteristics are provided in Supplementary Table 1.

3.3. Prediction model

3.3.1. Risk factors associated with anastomotic leakage

A total of 1319 (10%) patients were diagnosed with AL. The following parameters were associated with AL in univariable analysis: gender, age, BMI, ASA classification, neoadjuvant radiotherapy, clinical T-stage, approach, procedure, tumor height from anal verge, and deviating ileostomy. Univariable analyses are shown in Table 1.

The definitive multivariable model identified the following variables to independently increase risk for AL: male gender (OR 1.62), ASA III/IV (OR 1.33), BMI (OR 1.11, for each 5 kg/m^2 increase), short-course radiotherapy 5 × 5 Gy (OR 1.35), chemoradiotherapy (OR 1.11), and clinical T-stage (T1; reference, T2 (OR 1.12), T3 (OR 1.35), T4 (OR 1.15)). In addition, the following variables reduced the risk for AL: increase in age (non-linear, overall $p = 0.0005$), construction of a deviating stoma (OR 0.45), and greater distance between location of the tumor and the anal verge (OR 0.89 for each increase in millimetres). Outcomes of multivariable analyses are shown in Table 2. The model had a C-index of 0.664 for prediction of AL and the Brier score was 0.087. After cross-validation the C-index remained 0.658 and the Brier score remained 0.087. Calibration is plotted in Fig. 1. In patients operated before 2018 (AL recorded up to 30 days) the model had a c-index of 0.653. A c-index of 0.683 was found in those operated after 2018 (AL recorded up to 90 days).

3.4. Development of risk-stratification score

A point weighted risk-stratification score for AL after reconstructive rectal cancer surgery was generated by point estimates obtained from the final multivariable model (Table 2). In addition, a nomogram was composed (Fig. 2). Risk to develop AL was calculated for the three tertiles of patients in the dataset. Prevalence of AL was noted to be 5.0% among patients with a score of 0–138 (low risk), 8.5% among patients scoring 138–165 (intermediate risk), and 16.4% among patients scoring 165 and higher (high risk, $p < 0.001$, Supplementary Fig. 1).

Table 1
Baseline & (post)operative characteristics.

		No anastomotic leakage	Anastomotic leakage	*P-value*
		11856 (90)	1319 [10]	
Gender	Male	7280 (88)	945 [12]	<0.001
	Female	4572 (92)	374 [8]	
Age (years)		66.0 [59.0, 73.0]	65.0 [58.0, 71.0]	<0.001
BMI (kg/m^{Dev})		25.7 [23.5, 28.4]	25.9 [23.8, 28.7]	0.012
ASA score[c]	I/II	10,291 (90)	1108 [10]	0.005
	III/IV	1563 (88)	211 [12]	
Comorbidities	Myocardinfarction in history	532(88)	71(12)	0.144
	Heart disease	168(90)	18(10)	0.904
	Peripheral vascular disease	459(90)	48(10)	0.707
	Lung disease	1022(89)	124(11)	0.354
	Cerebrovasulair accident (CVA)	668(90)	71(10)	0.753
	Diabetes	1390(90)	146(10)	0.498
	Kidney disease	186(88)	25(12)	0.417
(Chemo)Radiotherapy	No	4936 (90)	524 [10]	0.036
	5x5 Gray	3691 (89)	459 [11]	
	50 Gray and chemotherapy	3074 (91)	327 [10]	
cT Stage	T1	567 (92)	50 [8]	0.005
	T2	3246 (91)	328 [9]	
	T3	6824 (89)	831 [11]	
	T4	640 (92)	59 [8]	
Tumor height from anal verge, mm		100.0 [70.0, 120.0]	80.0 [50.0, 100.0]	<0.001
Approach	Open	1928 (91)	196 [9]	<0.001
	Laparoscopic	8614 (90)	914 [10]	
	Transanal and open	4 (67)	2 [33]	
	Transanal Minimally Invasive Surgery[b]	96 (96)	4 [4]	
	Transanal and laparoscopic	628 (83)	128 [17]	
	Robot-assisted	502 (88)	66 [12]	
Additional resection	No	11,495 (90)	1285 [10]	0.667
	Advanced	190 (92)	17 [8]	
	Limited	161 (90)	17 [10]	
Type of resection	Elective	11,765 (90)	1312(10)	0.483
	Elective after treatment with decompromosing stent or deviating stomy	85(92)	7(8)	
Tumor related complications prior to surgery[a]	No	9931(90)	1109(10)	0.844
	Yes	1916(90)	210(10)	
Surgical procedure	Low anterior resection	10,420(91)	1178(10)	<0.001
	Partial Mesorectal Excision	1177(91)	119(9)	
	Subtotal colectomy	28(88)	4(12)	
Deviating Stoma	No	5550 (88)	769 [12]	<0.001
	Yes	6303 (92)	550 [8]	

[a] (i.e. anemia, obstruction, abcess.
[b] Transanal Minimally Invasive Surgery was followed by Total Mesorectal Excision.
[c] American Society of Anesthesiology score.

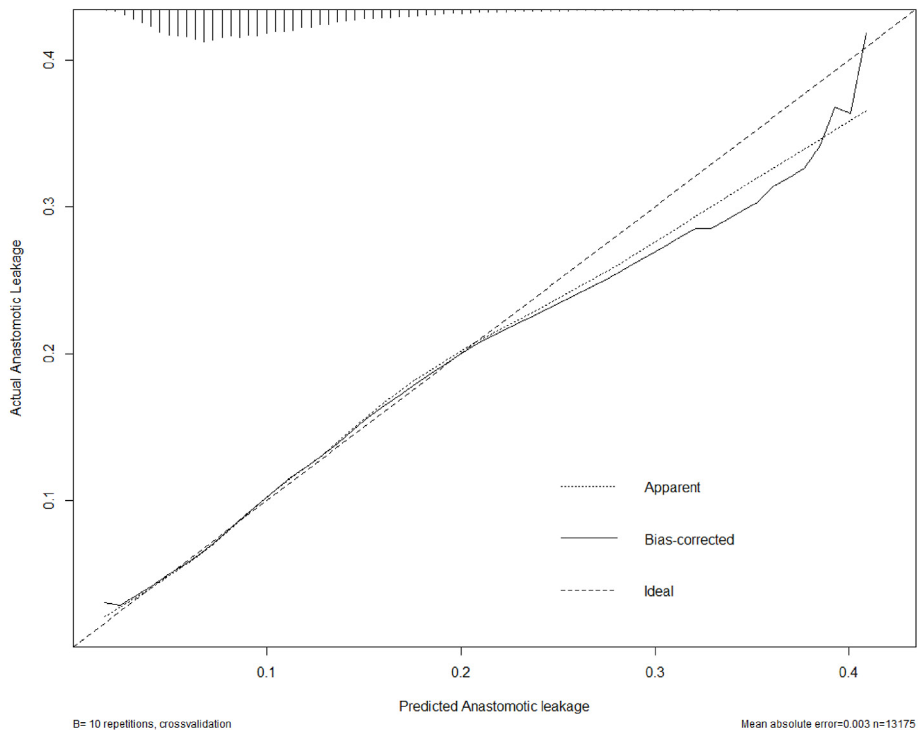

Fig. 1. Calibration model performance
Apparent: AL predicted versus actually observed. The model overvalues slightly when AL is predicted to be >20%, which means that the model predicts slightly higher AL rates then actually observed. Bias-corrected: AL predicted versus actually observed after cross-validation.

Table 2
Multivariable Cox proportional regression analysis.

	Points	Odds ratio	95% CI	p-value
Male gender	26	1.62	(1.79–9.17)	<0.0001
Age	[a]	[a]	[a]	0.005
BMI, 5 kg/m2	6	1.11	(1.03–1.19)	0.0046
Stoma				
None	43	Ref	–	–
Deviating Stoma	0	0.45	(0.39–0.51)	<0.0001
ASA III/IV	15	1.33	(1.13–1.57)	0.0007
Radiotherapy				0.0002
None	0	Ref	–	–
5x5 Gy	16	1.35	(1.17–1.56)	<0.0001
50 Gray and chemotherapy	5	1.11	(0.93–1.32)	0.2504
cT Stage				0.0273
T1	0	Ref	–	–
T2	6	1.12	(0.81–1.53)	0.5013
T3	16	1.35	(0.99–1.84)	0.0669
T4	7	1.15	(0.75–1.70)	0.5687
Tumor height from anal verge, mm	−6	0.89	(0.87–0.90)	<0.0001

[a] Variable due to restricted cubic splines; 0.08 x Age - 0.001 x Age ^ 3 + 0.003 x Age ^ 3−0.001 x Age ^ 3; C-index of 0.66365 and Brier score of 0.0872.

4. Discussion

Anastomotic leakage remains one of the most dreadful complications within colorectal surgery. Over the last decades AL rates have been reduced, although the average AL rate of rectum surgery is still two times higher than colon surgery [4,7–9]. Given the potential morbidity and even mortality after a leakage, appropriate risk-stratification before surgery is critical to help better predict AL. Using a cohort of 13.175 patients who underwent an elective rectum resection for cancer, the present study developed an accurate pre-operative risk-stratification tool to identify patients at high risk for AL. With the inclusion of a deviating ileostomy in the model, the risk-stratification tool transparently shows the risk reduction which could be gained by construction of such a stoma. Moreover, the model can be used for patient counselling prior to their operation. Identification of high-risk patients may assist during shared decision making, when patients and their physician plan to create an anastomosis (with or without deviating ileostomy) or maybe choose for a permanent colostomy instead.

Previous studies have identified multiple risk factors for AL after rectum surgery but failed to produce an established prediction model. Attempts have been made but most prediction models lacked accuracy or applicability to a preoperative clinical setting. For example, Watanabe et al. introduced a prediction model for AL after rectum surgery and mainly focused on preoperative baseline characteristics without considering imaging related data such as

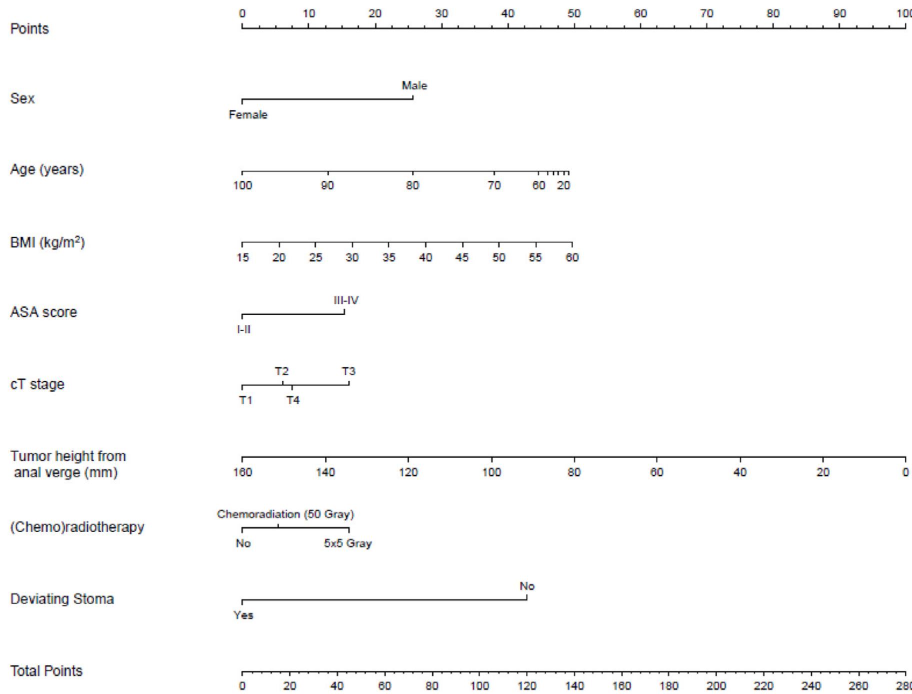

Fig. 2. Nomogram.

tumor size and distance to the anal verge [16]. Eventually a c-index of 0.625 for AL was found, which is lower than the c-index in the present study. Zheng et al. included preoperative and perioperative variables, including duration of operation, anastomotic bleeding and surgical approach [28]. Obviously, the addition of these extra variables increased discriminative power of the model, and the authors reported a c-index of 0.722. However, perioperative variables preclude use of the model during shared decision making before surgery. The Rectal Anastomotic Leak score used variables that were comparable to those used in the present study [18]. Nevertheless, the reported c-index was 0.585, which can be considered a relatively poor model. The candidate risk factors in the present study were selected by reviewing literature. Noteworthy, a higher age was associated with a risk reduction in the model. Although counter intuitive, this finding is supported by previous studies [30–35]. An experimental study found that aging tissues develop more chronic inflammation without overt infection, which may contribute to more subclinical-instead of severe morbidity in elderly patients [30,36]. Subclinical AL was not reported in the current database. Other explanations include selection of the fittest and survivor bias [30]. Despite the 'protective' effect of age, mortality rates of elderly patients following AL increases drastically [30,37,38]. Clinical T stage three was associated with a higher risk for AL compared to patients with a clinical T stage four carcinoma. Bias might have been introduced by preoperative selection of patients with favourable expected outcome, while high-risk patients with a T4 staged carcinoma were excluded from surgical curative treatment. The finding that short-course radiotherapy (5 × 5Gy) is associated with a larger increase in risk for AL compared to chemoradiation has been described previously [39,40].

Within the current prediction model, deviating ileostomy was included. Although this is an operative variable, the decision to construct a stoma is often based on preoperatively available characteristics. Absence of a deviating ileostomy was pointed out as a strong predictor for AL requiring reintervention. A deviating stoma could effectively prevent patients from developing severe symptomatic AL which has been demonstrated previously [41–43]. Importantly, it should be considered that AL on itself is not reduced but severe morbidity requiring reinterventions is minimized [44]. Despite the potential benefits, it should be taken into account that a stoma introduces the risk for additional complications during reversal and could have significant impact on quality of life [1,45]. Therefore, the current risk-stratification tool might help to identify those who will potentially benefit from a deviating stoma and preserve patients who do not need a stoma due to low risk.

The present study had several limitations that need to be addressed. Only leakages that required reintervention were considered in the definition of AL, and subclinical leakages, which may be prevalent especially among patients with a deviating ileostomy, were not registered. Furthermore, the definition slightly changed during the study period. AL was recorded up to 30 days postoperatively in patients operated until 2017 and up to 90 days since 2018, after it was shown leakages are also diagnosed beyond 30 days [24]. Nonetheless, validation showed comparable model performance in both study periods, with even slightly better discriminative power for patients with a 90-day follow-up. Although this study used a comprehensive list of patient characteristics and imaging variables, a few potential risk factors, such as corticosteroid use and smoking, were not available in the DCRA database and therefore not considered in the model. It is recommended to subject the model to external validation on another population-based repository.

Despite these limitations, the strength of the present study was that results were based on a nationwide cohort representing a population which could not be affected by selection bias based on required informed consent. In addition, the large sample size induces statistical power to detect differences between risk factors and generate an accurate prediction model. Furthermore, heterogeneity was minimized by considering rectum surgery for cancer only. Finally, all parameters included in the risk-stratification tool are commonly known, clearly defined, and therefore easily accessible in a clinical setting. With a c-index <0.7 the prediction model lacks discriminative value. Based on the strengths described, it should be considered that the current model has approached the maximum discriminative value which could be obtained from the currently known, preoperatively available, parameters associated with AL. However, there is much to gain in terms of discriminative value which means that there is still a lot to discover with regards to the pathophysiology of AL. Therefore, the colorectal community should strive for identification of additional (out of the box) factors that could compromise anastomotic healing such as expertise, microbiomes, macro/micro vascular calcification, or modifiable risk factors (i.e. preoperative haemoglobin, hyperglycemia, antibiotic prohylaxis and analgesia) [46–48].

The present study generated a discriminative prediction model based on preoperatively available variables. The proposed score can be used for patient counselling and risk-stratification before undergoing rectal resection for cancer.

CRediT authorship contribution statement

V.T. Hoek: Conceptualization, Methodology, Investigation, Data Validation, Writing – original draft. **S. Buettner:** Data curation, Methodology, Investigation, Writing – original draft. **C.L. Sparreboom:** Conceptualization, Data curation, Methodology, Investigation, Writing – original draft. **R. Detering:** Data curation, Methodology, Investigation, Writing – review & editing. **A.G. Menon:** Conceptualization, Methodology, Writing – review & editing, Supervision. **G.J. Kleinrensink:** Conceptualization, Methodology, Writing – review & editing, Supervision. **M.W.J.M. Wouters:** Conceptualization, Methodology, Writing – review & editing, Supervision. **J.F. Lange:** Conceptualization, Methodology, Writing – review & editing, Supervision. **J.K. Wiggers:** Conceptualization, Methodology, Data curation, Investigation, Writing – original draft, Supervision.

Declaration of competing interest

On behalf of the REPAIR research group of the Erasmus University Medical Center (Rotterdam, the Netherlands), I am very pleased to send you this manuscript entitled "A preoperative prediction model for anastomotic leakage after rectal cancer resection based on 13.175 patients" for peer review to *European Journal of Surgical Oncology* on behalf of the following authors V.T. Hoek, M.D, S. Buettner, M.D. Phd.D, C.L. Sparreboom M.D. Ph.D., R. Detering, M.D. Ph.D., A.G. Menon, M.D. Ph.D., G.J. Kleinrensink Ph.D., M.W.J.M. Wouters, M.D. Ph.D., J.F. Lange, M.D. Ph.D., J.K. Wiggers M.D. Ph.D. All authors have read and complied with the author guidelines and did declare there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2022.06.016.

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