The American Journal of Surgery 217 (2019) 465–468

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Factors associated with noncomplete mesorectal excision following surgery for rectal adenocarcinoma

Ipek Sapci, Jorge Silva Velazco, Xhileta Xhaja, Alexandra Aiello, Emre Gorgun, Luca Stocchi, Conor P. Delaney, Scott R. Steele, Michael A. Valente*

Department of Colorectal Surgery, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, OH, USA

ARTICLE INFO

Article history:
Received 27 July 2018
Received in revised form
9 October 2018
Accepted 13 October 2018

Keywords:
Mesorectal grade
Complete mesorectum
Total mesorectal excision
Abdominoperineal resection

ABSTRACT

Background: The completeness of the resected mesorectum is a quality metric in rectal cancer surgery and has been related to oncological outcomes. Our aim was to identify variables associated with non-complete mesorectal excision and determine any effect on overall survival.

Methods: Consecutive patients who underwent curative intent surgery for rectal adenocarcinoma (2009–2016) were identified from a prospectively-maintained institutional database. Patients were grouped according to their mesorectal grade: complete, near-complete and incomplete. Multivariate analysis was performed to identify the association between various patient, disease and surgeon-related characteristics and mesorectal grading. Log-rank tests were used to evaluate any difference in overall survival between the groups.

Results: 689 patients met inclusion criteria. Demographics and perioperative variables were comparable between the groups. On multivariate analysis, abdominoperineal resection, and involved circumferential resection margin were significantly associated with non-complete mesorectum. Finally, patients with non-complete mesorectal grading have approximately twice the hazard of death compared to those with complete mesorectal grading.

Conclusions: Several factors are associated with a non-complete mesorectal excision. Non-complete mesorectal grade is associated with decreased survival.

Introduction

The term and concept of total mesorectal excision (TME) have become standard in rectal cancer surgery since the 1980s. Reports have shown that TME has resulted in decreased local recurrence rates and it has been well established as the standard operative treatment for radical surgery for rectal cancer.[1]

The role of the pathological examination of the resected specimen has gained increasing significance since its suggested use as an important quality control parameter in rectal cancer surgery.[2] Nagtegaal et al. stressed the importance of macroscopic evaluation of the mesorectum based on the results of the Dutch TME trial.[2] This was followed by multiple studies and TME became widely accepted and its macroscopic assessment was recognized as an integral part of the surgical quality evaluation, requiring multidisciplinary collaboration.[3] Previous studies on mesorectal grading mostly focus on its effect on local recurrence rates with few focusing on factors affecting the grading and survival.[3–7]

We hypothesized that a complete mesorectum was associated with improved oncological outcomes. In addition, identifying the potential risk factors that are associated with incomplete excision may help surgeons improve patient outcomes. Therefore, the aim of our study was to identify any potential risk factors that may be associated with a non-complete mesorectum. The secondary aim was to determine any effect of mesorectal grading on overall survival.

Methods

We included all patients (clinical stages 1–4) who underwent curative-intent TME for middle and distal third rectal adenocarcinoma between 2009 and 2016. Patients were identified from a prospectively maintained institutional database after obtaining Institutional Review Board approval. Patients who had incomplete

* Corresponding author. 9500 Euclid Avenue, Desk A-30, Cleveland, OH, 44195, USA.
E-mail address: valentm2@ccf.org (M.A. Valente).

https://doi.org/10.1016/j.amjsurg.2018.10.051
0002-9610/

pathology reporting, synchronous tumors, who underwent surgery for recurrent rectal cancer and patients who had histopathological confirmation of other than adenocarcinoma were excluded from the study. Tumors located in the upper rectum (>11 cm from anal verge) were also excluded from the study group.

Patients were categorized into three previously defined groups according to their mesorectal grading: complete, near-complete and incomplete according to the parameters suggested by Nagtegaal et al.[2]. Complete mesorectum specimen was described as the intact, smooth, regular outer surface of the mesorectum with no defects deeper than 5 mm. Specimens with moderate bulk and irregular surfaces were grouped into near-complete and specimens with little bulk and that show coning with defects reaching muscularis propria were grouped as incomplete. All specimens were evaluated and graded by gastrointestinal pathologists using a standardized pathology synoptic report. Separate analyses were also performed by combining near complete and incomplete mesorectal grading as a "non-complete" mesorectum group.

Statistical analysis

Summary statistics are reported as mean ± standard deviation or median [25th percentile, 75th percentile] for continuous factors and as frequency (column %) for categorical factors. Univariate analyses were conducted to evaluate the association between patient factors and mesorectal grading completeness as well as pathologic factors and mesorectal grading completeness. The univariate analysis was done for the three groups (complete, near-complete and incomplete) and two groups (complete, non-complete) separately. A Pearson's chi-square test or Fisher's exact test were used for categorical factor, and ANOVA or the Kruskall-Wallis test was used for continuous factors.

A multivariable logistic regression model was also used to analyze the risk of non-complete grading. These variables included: distance of the tumor from the anal verge, circumferential resection margin (CRM), distal margin, restorative procedure, procedure type (open, laparoscopic, robotic), pathological differentiation, and final pathological stage were considered for selection into the model, and a backwards selection procedure with alpha = 0.1 stay criteria was used to determine the final model.

Median follow-up is reported in months. Kaplan-Meier curves were plotted to compare overall survival across the various mesorectal grading groups. A multivariable Cox proportional hazard model was created to compare overall survival between complete and non-complete grading groups after adjusting for potential confounders. All analyses were performed using SAS (version 9.4, The SAS Institute, Cary, NC), and p-values < 0.05 were considered statistically significant.

Results

The study group included 689 patients with a mean age of 58.7 (range, 28–93 years), 65.8% male. Median follow-up was 41 months. Overall, 90% (622/689) of mesorectum specimens were complete, 6% (40/689) near-complete and 4% (27/689) incomplete. Body mass index (BMI), age, gender, estimated blood loss (EBL), and length of surgery were not associated with non-complete mesorectal grade and were similar between the groups (all P=NS). Additionally, clinical and pathologic TNM staging, the utilization of neoadjuvant therapy or operative approach (open vs. laparoscopic vs. robotic) were not associated with a non-complete mesorectal grade (Table 1).

On multivariate analysis, distal tumors (0–5 cm from the anal verge), non-restorative procedure, and positive circumferential

Table 1
Analysis of variables associated with non-complete mesorectal excision.

Variable	Complete n = 622	Non-complete n = 67	p-value	Complete n = 622	Near Complete n = 40	Incomplete n = 27	p-value
Age	58.7 ± 12.5	61.5 ± 11.3	0.077	58.7 ± 12.5	61.7 ± 9.8	61.2 ± 13.5	0.21
Gender (Male)	414 (66.6)	40 (59.7)	0.26	414 (66.6)	26 (65)	14 (51.9)	0.29
BMI, kg/m^2	28.2 ± 6	28.4 ± 8.1	0.8	28.2 ± 6	29.4 ± 9	26.9 ± 6.3	0.25
Neoadjuvant therapy (yes)	380 (61.8)	47 (71.2)	0.13	380 (61.8)	29 (74.4)	18 (66.7)	0.26
Clinical Stage							
I	84 (16.4)	7 (12.3)	0.74	84 (16.4)	5 (14.3)	2 (9.1)	0.81
II	123 (24)	17 (29.8)		123 (24.0)	11 (31.4)	6 (27.3)	
III	259 (50.6)	28 (49.1)		259 (50.6)	15 (42.9)	13 (59.1)	
IV	46 (9)	5 (8.8)		46 (9.0)	4 (11.4)	1 (4.5)	
Operation time (minutes)	232.4 ± 90.2	250 ± 110.5	0.15	232.4 ± 90.2	266.4 ± 122.3	225.0 ± 86	0.078
EBL (ml)	453 ± 846.6	475.3 ± 509.2	0.83	453 ± 846.6	450.8 ± 499.5	511.7 ± 530.8	0.94
Distance from anal verge (cm)	6.3 ± 4	4.7 ± 3.8	0.004	6.3 ± 4	5.1 ± 4.4	4.3 ± 2.8	0.013
Restorative procedure			<0.001				<0.001
Yes	463 (74.7)	24 (35.8)		463 (74.7)	17 (42.5)	7 (25.9)	
No	157 (25.3)	43 (64.2)		157 (25.3)	23 (57.5)	20 (74.1)	
Procedure Type			<0.001				<0.001
LAR	455 (73.2)	23 (34.3)		455 (73.2)	16 (40)	7 (25.9)	
APR	148 (23.8)	42 (62.7)		148 (23.8)	23 (57.5)	19 (70.4)	
Surgical approach			0.93				0.83
Open	383 (61.6)	41 (61.2)		383 (61.6)	25 (62.5)	16 (59.3)	
Laparoscopic	157 (25.2)	16 (23.9)		157 (25.2)	11 (28.2)	5 (18.5)	
Lap-converted	2 (0.32)	0 (0)		2 (0.32)	0 (0)	0 (0)	
Robotic	80 (12.9)	10 (14.9)		80 (12.9)	4 (10.3)	6 (22.2)	
Circumferential resection margin positivity	29 (4.7)	13 (19.4)	<0.001	29 (4.7)	6 (15)	7 (25.9)	<0.001
Pathological Stage			0.35				0.79
I	188 (30.6)	14 (21.9)		188 (30.6)	8 (21.1)	6 (23.1)	
II	124 (20.2)	19 (29.7)		124 (20.2)	11 (28.9)	8 (30.8)	
III	200 (32.6)	20 (31.3)		200 (32.6)	12 (31.6)	8 (30.8)	
IV	45 (7.3)	6 (9.4)		45 (7.3)	4 (10.5)	2 (7.7)	
pCR	57 (9.3)	5 (7.8)		57 (9.3)	3 (7.9)	2 (7.7)	

Values are reported as mean ± SD or absolute values (%). BMI: Body Mass Index; EBL: estimated blood loss; LAR: low anterior resection; APR: abdominal perineal resection; pCR: pathologic complete response.

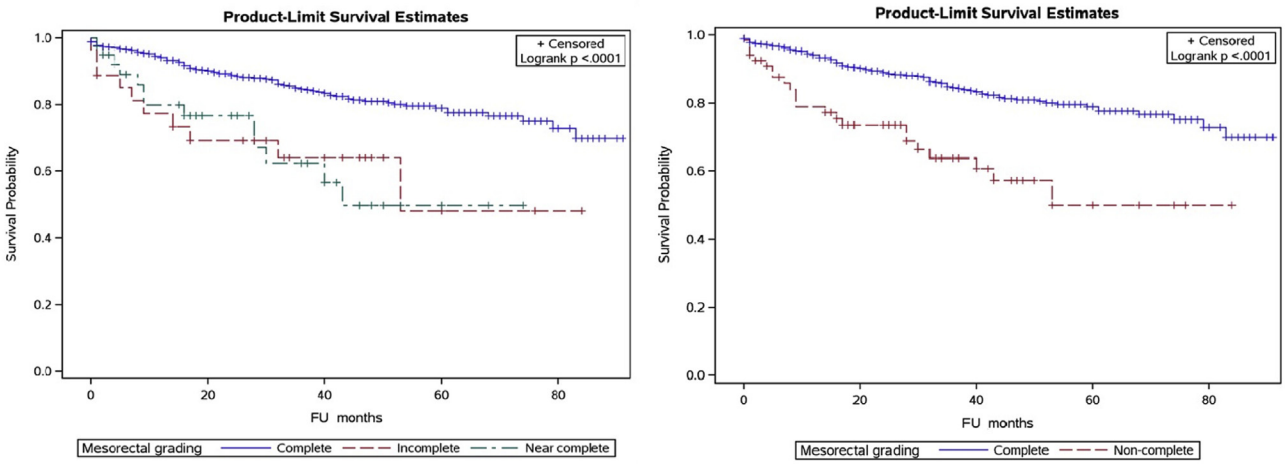

Fig. 1. Kaplan-Meier curves for overall survival.

resection margin (CRM) were significantly associated with non-complete mesorectum. Patients undergoing an abdominoperineal resection were five-fold more likely to have non-complete grading compared to patients undergoing a low anterior resection [OR: 0.20 (CI: 0.11–0.38)]. Additionally, patients with a positive CRM had a higher rate of non-complete mesorectal grade compared to those patients with a negative CRM [OR: 2.5 (1.05, 6.1)]. Finally, patients with non-complete mesorectal grading have approximately twice the hazard of death compared to those with complete mesorectal grading [HR: 2.0 (1.2, 3.3)] (Fig. 1).

Discussion

Our study reports that an overall complete mesorectal grade of 90% can be accomplished and reveals abdominoperineal resection and lower third tumors to be significant risk factors that are associated with a non-complete mesorectal grade. Circumferential resection margin positivity was also associated with non-complete mesorectal grading. Additionally, we found that a non-complete mesorectal grade to be related to lower overall survival in this patient population.

Abdominoperineal resections were five-fold more likely to have non-complete mesorectal grading based on our results. In addition, tumors closer to the anal verge were significantly more common in the non-complete mesorectum group. The effect of APR has been investigated and it has been related to worse mesorectal quality.[3,5–7] In a study by Garcia-Granero et al., APR was identified as the single variable associated with inadequate mesorectal excision. Furthermore, they found that in lower third tumors, a non-complete mesorectum rate of 36% was achieved was when APR was employed.[7]

Maslekar et al. and Lino-Silva et al. also reported similar results with APRs and found it to be associated with a worse mesorectal grade.[3,4] This correlation may be explained by greater difficulty of surgery in the most distal part of the rectum and possibly due to the narrow and complex confines of the pelvis.[3]

Nagtegaal et al. defined the completeness of the mesorectum as a quality parameter based on the results of the Dutch TME trial and found that patients with an incomplete mesorectum were more likely to undergo APR and to have positive circumferential resection margins.[2] Similar to our study, they report higher rates of survival in the complete mesorectum group. It must be noted that Nagteggal and colleagues combined the complete and the near-complete group and analyzed it versus the incomplete group. However, they stated that optimal surgery (complete mesorectum) must be the goal; therefore, based on this statement and the number of patients in each of our groups, we designed our study to compare optimal vs. non-optimal specimens.

Other factors that were emphasized in previous studies are the surgical approach and demographic factors.[5,6,8–10] Factors that affect the achievement of an adequate TME specimen were listed as female gender, BMI and low rectal cancer.[5] Two meta-analyses also concentrated on the effect of surgical approach on the mesorectal grade and their results favored open surgery to achieve a complete mesorectum.[8,9] In our study, we did not find any statistical difference regarding BMI, gender, or the surgical approach relating to the completeness of the mesorectum.

In line with previous studies, patients with positive circumferential margin (CRM) had 2.5 times the risk of having non-complete mesorectum, and in our study, patients with positive CRM were more common in the non-complete group.[5,6] CRM is an established quality parameter in rectal cancer surgery, and it is closely associated with recurrence rates and survival.[11] Reports also suggest that the mesorectum quality can be a predictor of CRM involvement[3] and it is thought that achieving a high-quality complete mesorectum specimen makes it less likely to have a positive CRM. We believe that this relation requires mesorectal grade to be evaluated alongside CRM and more widespread reporting of mesorectum quality should be implemented.

The precision of the surgical technique is critically important for overall patient survival.[3] Association between non-complete mesorectum and worse overall survival was previously shown.[2] In our study patients with non-complete grading had twice the hazard of death which highlights the importance of this parameter. However, longer follow-up may be necessary to validate this finding.

Limitations of our study include the retrospective nature of the data and the absence of individual surgeon data as a potential factor in the analysis. In our study we included surgeries performed by 25 different surgeons over the time period, therefore, it was not possible to relate possible differences in mesorectal grade to individual surgeons. Yet collectively, we were able to achieve a completion rate of 90%. In addition to these factors, complete mesorectum rate is higher in our group compared to the known literature,[9] which might have confounded the comparison due to the small patient numbers in the non-complete group. However, the mesorectum were graded by GI-specific pathologists blinded to individual surgeon variability.

In conclusion, having an abdominoperineal resection and having a positive circumferential resection margin were independent risk factors associated with a non-complete mesorectal excision. Non-complete mesorectal excision is also related to a decrease in overall survival. The goal of curative intent rectal cancer surgery should be to achieve a complete mesorectal grade and this may be used as a surrogate for quality surgery. Surgical technique should be optimized to attain a complete mesorectum in patients with low rectal cancer and patients who are undergoing abdominoperineal resection. These factors should be considered when caring for patients with rectal adenocarcinoma.

Conflicts of interest

The authors have no conflicts of interest or financial ties to disclose. Authors of the manuscript are:: Ipek Sapci, MD, Jorge Silva Velazco, MD, Xhileta Xhaja, MD, Emre Gorgun, MD, Luca Stocchi, MD, Scott R. Steele, MD, and Michael A. Valente, DO.

References

1. Heald RJ, Ryall RDH. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet*. 1986. https://doi.org/10.1016/S0140-6736(86)91510-2.
2. Nagtegaal ID, van de Velde CJH, van der Worp E, et al. Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. *J Clin Oncol*. 2002;20(7):1729–1734. https://doi.org/10.1200/JCO.2002.07.010.
3. Maslekar S, Sharma A, MacDonald A, Gunn J, Monson JRT, Hartley JE. Mesorectal grades predict recurrences after curative resection for rectal cancer. *Dis Colon Rectum*. 2007;50(2):168–175. https://doi.org/10.1007/s10350-006-0756-2.
4. Lino-Silva LS, García-Gómez MA, Aguilar-Romero JM, et al. Mesorectal pathologic assessment in two grades predicts accurately recurrence, positive circumferential margin, and correlates with survival. *J Surg Oncol*. 2015;112(8):900–906. https://doi.org/10.1002/jso.24076.
5. Leonard D, Penninckx F, Fieuws S, et al. Factors predicting the quality of total mesorectal excision for rectal cancer. *Ann Surg*. 2010;252(6):982–988. https://doi.org/10.1097/SLA.0b013e3181efc142.
6. Jeyarajah S, Sutton CD, Miller a S, Hemingway D. Factors that influence the adequacy of total mesorectal excision for rectal cancer. *Colorectal Dis*. 2007. https://doi.org/10.1111/j.1463-1318.2007.01256.x.
7. García-Granero E, Faiz O, Muñoz E, et al. Macroscopic assessment of mesorectal excision in rectal cancer. *Cancer*. 2009;115(15):3400–3411. https://doi.org/10.1002/cncr.24387.
8. Creavin B, Kelly ME, Ryan E, Winter DC. Meta-analysis of the impact of surgical approach on the grade of mesorectal excision in rectal cancer. *Br J Surg*. 2017;104(12):1609–1619. https://doi.org/10.1002/bjs.10664.
9. Martínez-Pérez A, Carra MC, Brunetti F, de'Angelis N. Pathologic outcomes of laparoscopic vs open mesorectal excision for rectal cancer. *JAMA Surg*. 2017. https://doi.org/10.1001/jamasurg.2016.5665.
10. Madbouly KM, Hussein AM, Abdelzaher E. Long-term prognostic value of mesorectal grading after neoadjuvant chemoradiotherapy for rectal cancer. *Am J Surg*. 2014;208(3):332–341. https://doi.org/10.1016/j.amjsurg.2013.10.023.
11. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? *J Clin Oncol*. 2008;26(2):303–312. https://doi.org/10.1200/JCO.2007.12.7027.