Outcome assessment of developments in rectal cancer treatment

Outcome assessment of developments in rectal cancer treatment: a patient and surgical perspective

Vincent Maurice Meyer

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voor pap en mam

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CHAPTER 1

General introduction and thesis outline

1

INTRODUCTION

Each year, there are approximately 700.000 new cases of rectal cancer worldwide.[1] Rectal cancer is different from colon cancer because it has specific challenges, mainly due to its location deep in the pelvis and repercussions of treatment on anorectal and urogenital function. Survival has increased in the last decades with improved combinations of such treatment modalities as surgery, radiotherapy and systemic therapy.[2,3] However, colon and rectal cancer combined remains in the top two in terms of cancer related mortality and incidence in Europe.[4]

Surgical treatment of rectal cancer

Up to the 19th century, colorectal cancer surgery was limited to the creation of a defunctioning stoma. In 1826, Lisfranc was the first surgeon to perform a successful perineal resection of a rectal tumor. From then, perineal resections were performed for rectal cancer; usually with considerable morbidity and mortality for the patient.[5] Besides major perioperative risk for the patient, more proximal tumors and recurrence remained a problem with a perineal approach. William Miles, an English surgeon working in London, noticed that most of the recurrences in his patients found their origin upwards in the mesorectum. Therefore, he concluded that the rectum should be excised in a large cylindrical form including the lymph nodes. He combined a perineal resection with an abdominal approach ('Miles's operation') and in doing so introduced the abdominoperineal resection in 1908, eventually drastically reducing recurrence rates from practically 100% to 30%.[6] His work would later be collaborated by Dukes, who demonstrated that lymph node spread impacted poorly on local control. Eventually with better understanding of pelvic anatomy, Heald would introduce the Total Mesorectal Excision propagating sharp dissection along the identifiable plane of the circumferential mesorectum lowering recurrence rates from 30 to 5-8%.[7]

Meanwhile since the 18th century, mostly battlefield surgeons had been experimenting with bowel anastomosis after penetrating trauma, but with little success. For a long time, rectal cancer treatment equaled formation of a stoma. However, several techniques were developed to create continuity of bowel. The pull through procedure described by Hoche egg in 1808, later popularized after modification by Babcock and Bacon, became common in the 20th century in Anglo-Saxon countries. It allowed for a direct anastomosis without compromising the oncological principles of a radical resection introduced by Miles. After resection of the rectum, the colon would be 'pulled through' the anus and anastomosed. Of course, functional problems occurred frequently and advancing anatomical knowledge led to improved results with sphincter preservation. In 1948, Claude Dixon published his series of sphincter preserving rectal resections for upper rectal cancer, limiting perioperative mortality rate to 2.6%.[8] From here on, sphincter preservation became generally accepted. Another important step forward in anastomotic technique was the development of circular staplers in the 70's that allowed creation of a 'low' anastomosis in more distally occurring tumors and more sphincter preserving techniques.

Although the oncological outcome has drastically improved in the last 100 years with these techniques, the radical nature of rectal resection still has great impact on quality of life today as bowel, sexual and urinary function often become severely compromised. Especially in the setting of the current improved survival after rectal cancer, this quality of life element is becoming increasingly important.[9]

Neo-adjuvant therapy

The first attempts to treat rectal cancer with radiotherapy were reported in the early 20th century, when surgery was still considered a salvage procedure, restricted by limited anesthetic options and high morbidity.[10] The first documented treatment of radiotherapy for rectal cancer was reported in 1917, by Janeway and Quick, through application of radon beads into the tumor providing a macroscopic tumor response.[11] Because anesthesiologic and surgical techniques improved, surgery became the preferred treatment option. Still, locally recurrent tumor remained a problem especially in large resected tumors. From the 1980's onwards, trials explored the additional benefit of radiation to surgery. Dosage, fractioning and timing differed among studies, but generally this multimodality treatment led to a decrease in local recurrence rate.[12–14] A large UK-based collective identified an almost 50% risk reduction in local recurrence if adjuvant radiotherapy were given to patients with an initially advanced tumor.[15] Two landmark trials with adjuvant radiotherapy and chemotherapy that showed a benefit of radiotherapy established its adjuvant use in the US.[16–18]

In the meantime Heald had developed the principle of TME surgery and showed excellent long-term disease-free survival of 78% at 10 years without radiotherapy.[2] It was hypothesized that highquality radical surgery was the cornerstone of rectal cancer treatment and radiotherapy could be a useful adjunct.[10] Finally, the Dutch TME trial and UK/Canadian MRC CR07 trial showed that preoperative radiation decreased the risk of local recurrence by 50%, even with optimal TME surgery but without survival benefit.[3,19] A large French study in 733 patients found even further improved local control (16% vs 8%) with the addition of 5-FU and chemoradiotherapy.[20] Further studies then strengthened the pre-operative use of (chemo) radiotherapy compared to post-operative, in terms of better local control, tolerability and side-effects.[19,21] Although radiotherapy improves the local control, there is a downside in an increased rate of functional problems: up to 50% of patients report bowel, bladder and autonomous nerve dysfunction after preoperative radiotherapy.[22] Therefore a more selective use of neo-adjuvant radiotherapy is recommended for high or intermediate risk tumors, as shown in the Dutch guidelines.[23]

Surgery and radiotherapy, on their own and combined as multimodality treatment, have considerably improved survival of patients with rectal cancer. Now that patients, even in more advanced stages, have a better and longer survival, attention should be focused on improving long term functional outcome.

Non operative treatment

While neo-adjuvant therapy and TME surgery have improved local control with recurrence rates below 10%, at the expense of long term functional problems, it has also been shown

that in up to 25% of patients no viable tumor is found in the resection specimen. Therefore, it is inferred that an appreciable number of patients underwent TME surgery (and its associated morbidity) without any benefit. In these patients with a complete pathological response, a local recurrence is rarely encountered and prognosis is excellent.[24] It is therefore hypothesized, that this specific group of patients is overtreated with radical surgery and could avoid surgery altogether. In the '90's, professor Angelita Habr-Gama started to omit surgery in a select group of patients with a clinical complete response after neo-adjuvant chemoradiation and showed that surgery is not superior to careful follow-up in these patients.[25] At first, this non-operative Watch and Wait approach was met with skepticism. However, other centers started to reproduce the excellent oncological outcome in this group of patients.[25,26] Furthermore, follow-up studies showed that patients with a complete clinical response had less often progression to distant disease and could still be treated with curative intent in case of a tumor regrowth.[25,26] Also, functional outcome is significantly better compared to TME and the avoidance of surgery is highly appreciated by patients.[27–29] Over the past few decades, non-operative treatment with careful follow-up has become an accepted modality for patients with a complete clinical response and has been recognized as a valid alternative in the Dutch colorectal carcinoma guideline.[23]

Clinical audit - surveys

Surgery in general has always been on the forefront of clinical auditing dating back as far as dr. Ernest Codman in the 1900's, who was the first surgeon to gather patient outcomes to improve daily practice.[30] Based in Boston USA, he opened the first hospital that published patient outcomes publicly every year. From then, the surgical clinical audit has developed to become a standard of care in many countries, often leading to improved outcomes as the Dutch Colorectal Audit has shown in the Netherlands.[31]

An important form of audit is the survey, which can come in many forms. Patient reported outcomes, as well as surgeon consensus, obtained through surveys give valuable insight in what we do and how we (should) do it. Surveys have improved the evaluation of surgeon clinical practice and monitoring of patient quality of life, and has become important in regulatory decision making.[32–34] A survey can be quick and cost-effective and has the potential to reach a large population. To be reliable, unbiased and discriminatory, certain criteria have to be adhered to.[35] Survey response is dependent on many factors; understanding these is crucial in minimalizing response bias and optimizing reliability of survey results in order to improve treatment.[36–38]. An important threat is non-response bias, which has the potential to skew results due to unwanted selection of respondents.[39] Extensive research into maximizing survey response, usually in the field of psychology, identified important features that can influence survey response. Dillman developed the 'Total Design Method' or 'TDM' which includes more than 30 steps to improve response rates in mail and telephone surveys. He developed a system that is used worldwide today and works through reducing the burden of a survey (short closed ending questions), personalizing it (cover letter, handsigned) and providing information on its relevance, leading to significantly higher response rates and therefore less selection bias.[40]

THESIS OUTLINE

The aim of this thesis is to assess the outcomes of new treatments in colorectal surgery from a patient and surgeon perspective. The chapters in this thesis are divided in three parts. **Part I** evaluates the surgical and oncological outcome of recent innovations in colorectal surgery. **Part II** focusses on the patient perspective in novel treatment strategies. **Part III** explores the variables that influence patient and surgeon response in survey studies.

PART I surgical and oncological outcome in novel treatment strategies

In **Chapter 2**, we investigate whether delayed TME surgery for regrowth or residual disease in a W&W program leads to an increase in hospital costs, surgical morbidity or decreased survival for those who 'fail'. In **Chapter 3**, we explore the use of a continued organ preservation strategy with a LE in the setting of regrowth in W&W. We hypothesize that LE can prevent unnecessary rectal resection and/or stoma in large number of patients without compromising on oncological or surgical outcome.

Finally, neo-adjuvant therapy leads to involution of the tumor, but also involution of the surrounding affected and non-affected lymph nodes. In **Chapter 4** we investigate the relationship between specimen lymph node count after chemoradiotherapy (CRTx) and outcome.

PART II patient perspective in novel treatment strategies

A Watch and Wait (W&W) protocol provides considerable functional benefit in those patients who progress to a complete clinical response. In **Chapter 5** we investigate whether delayed surgery for patients with a regrowth or residual disease after initial (near) complete response has a negative impact on quality of life. This is measured through the EORTC QLQ C-30 and CR-29, Cancer Worry Scale and Decision Regret scale questionnaires, which are validated in this sample. When patients receive a protective stoma after TME surgery for rectal cancer, it will affect their bowel function. **Chapter 6** examines if early closure has benefit in terms of bowel function and QoL.

PART III variables influencing response in surveys

Chapter 7 reports on the response rate in surgical survey studies. We attempted to provide a mean response rate that could be considered acceptable in the current era of declining response rate. Furthermore, we identified measurable variables that influence response rate in patient and surgeon surveys and provided a reference for future survey design and review. In **Chapter 8**, factors that influence survey response rate in colorectal surgery are identified. In colorectal surgery specifically, a malignancy negatively affects response rate which places more emphasis on adequate survey design. Survey mode and follow-up are increasingly important in this group. In **Chapter 9** we discuss these findings for medical students and surgical residents and propose a reporting guideline.

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PART I

Surgical perspective

CHAPTER 2

Delayed TME surgery in a watch and wait strategy after neoadjuvant chemoradiotherapy for rectal cancer: an analysis of hospital costs, surgical, and oncological outcomes

Vincent M. Meyer, M.D., Richtje.R. Meuzelaar, B.Sc., Ivonne J.H. Schoenaker, M.A.N.P., Jan-Willem B de Groot, M.D, Ph.D., Onne Reerink, M.D., Ph.D., Wouter H de Vos tot Nederveen Cappel, M.D., Ph.D., Geerard L. Beets, M.D., Ph.D.[5], Henderik L. van Westreenen, M.D, Ph.D.

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ABSTRACT

Background
A Watch & Wait strategy for patients with rectal cancer with a clinical complete response after neoadjuvant chemoradiotherapy is a valuable alternative for rectal resection. However, there are patients who will have residual tumor or regrowth during Watch & Wait.

Objective
The aim was to investigate safety and costs for patients who underwent delayed surgery after neoadjuvant chemoradiotherapy.

Design
This is a retrospective cohort study with prospectively collected data.

Setting
The study was conducted at a large teaching hospital.

Patients
Between Jan 2015 – May 2020, 622 new rectal cancer patients were seen of which 200 received neoadjuvant chemoradiotherapy. Ninety-four patients were included of which 65 patients underwent immediate surgery and 29 patients required delayed surgery after an initial Watch & Wait approach.

Main outcome measures
This included 30-day postoperative morbidity rate, hospital costs and two-year overall and disease-free survival.

Results
here was no difference in length of stay (9 vs 8, p = 0.83), readmissions (27.6% vs 10.0%, p = 0.10), surgical re-interventions (15.0% vs 3.4%, p = 0.16) and stoma free rate (52.6% vs 31.0%, p = 0.09) between immediate and delayed surgery groups. Hospital costs were similar in the delayed group (€11913 vs €13769, p = 0.89). Two-year overall survival (93% vs 100%, p = 0.23) and disease-free survival (78% vs 81%, p = 0.47) rates were comparable.

Limitations
Small sample size, follow-up time and retrospective design.

Conclusion
Delayed surgery for regrowth in a Watch & Wait program or for persistent residual disease after a repeated assessment is not associated with an increased risk of postoperative morbidity or a significant rise in costs compared to immediate total mesorectal

INTRODUCTION

The standard treatment for patients with locally advanced rectal cancer is neoadjuvant chemoradiotherapy (CRTx) followed by TME surgery.

This strategy yields good oncological results, with a local recurrence rate below 10%. However, TME surgery is a radical procedure that carries a significant risk of morbidity with immediate postoperative complications and long-term bladder-, bowel- and sexual dysfunction as well as the need for a definitive stoma.[1] In 20-30% of patients a clinical complete response (cCR) is achieved after CRTx. Habr-Gama et al showed in 2004 that a close surveillance program instead of TME surgery after CRTx is a safe alternative for TME surgery with good oncological outcome for patients with a clinical complete response (cCR).[2] Since then, evidence for the so called "Watch & Wait" (WW) is increasingly accepted as an alternative to TME surgery. Currently, the challenge lies in proper patient selection for a WW strategy as clinical response assessment with digital rectal examination, endoscopy and MRI is not completely accurate.[3–5] In the majority of reported series, 20-30% of patients with a cCR in a WW program will experience a regrowth during follow up.[6,7] On the other hand, there are patients with a good response who do not fulfill the criteria for a clinical complete response. This is labeled as a near complete response (nCR) and with further follow up some of these will become complete responses (whereas others will more clearly show residual disease). In a cohort of 49 patients with nCR at 8-10 weeks, 90% turned out to have a cCR at response assessment 6-12 weeks later.[8] In large tumors, it can even take 19-26 weeks to develop a cCR.[5] Therefore, with a single early response assessment many complete responders can be missed and repeated assessment is advocated to detect more complete responders. However, the drawback of this approach is that TME surgery for patients without a cCR or with a regrowth will be delayed. There is concern that delayed surgery can be accompanied by increased morbidity due to more post-radiation fibrosis and clinicians worry about the oncological safety.[6,9,10]

Two studies have reported that overall, a WW policy is cost effective compared to CRT and TME.[11,12] For patients who require delayed surgery, the additional cost of the follow up examinations is no longer offset by the cost saved by avoiding major surgery and a policy of repeated assessments in near complete responders could lead to an overall increase in cost.

The aim of this study is to present the surgical and oncological outcomes and to calculate hospital costs for patients who underwent delayed TME surgery in order to achieve a cCR after repeated response assessment in comparison with patients receiving CRT and immediate TME surgery.

MATERIALS AND METHODS

Patients

The repeated assessment strategy described below was implemented in our hospital in 2015 with the goal to identify more complete responders and to offer more patients a Watch & Wait approach. The study includes patients who received CRTx and TME surgery for adenocarcinoma of the rectum between Jan 2015-May 2020. Exclusion criteria were synchronous metastases, palliative treatment, other malignancy with ongoing active treatment or surveillance and delaying surgery for other reasons than a Watch & Wait approach. Patients receiving local excision after CRTX followed by TME surgery were included, while patients who did not receive salvage TME were excluded. Patients who received follow-up elsewhere or were lost to follow-up were excluded.

Study design

This study includes patients with locally advanced rectal carcinoma who received TME surgery following CRTx. Patients with an incomplete response at the assessment after CRT underwent immediate TME surgery and were defined as the immediate surgery group. Patients with an initial cCR who developed a regrowth or patients with a nCR who eventually did not progress to a cCR were defined as the delayed TME surgery group. This group of patients are part of the national prospective study "Wait-and-see" Policy for Complete Responders After Chemoradiotherapy for Rectal Cancer (clinicaltrials gov NCT03426397). Demographics, immediate vs delayed surgery, time interval between CRTx and operation, survival, occurrence of regrowth/metastases and inclusion in Watch & Wait strategy were collected prospectively. Other treatment data such as multidisciplinary meeting (MDM) outcome, clinic visits, laboratory tests, imaging and endoscopies were collected retrospectively. Data regarding (re)admission and complications were collected until 30 days postoperatively. The study was approved by the institutional review board of our institution.

Treatment and Follow-up

All patients identified with locally advanced rectal cancer underwent long course neoadjuvant chemoradiotherapy with curative intention (28 fractions of 1.8 Gy radiotherapy with twice daily bolus of Capecitabine 825mg/m^2. Patients were restaged with digital rectal examination, endoscopy, CT chest and abdomen and MRI 8 weeks after the end of neoadjuvant chemoradiotherapy. Clinical response was classified at the multidisciplinary colorectal oncology meeting as complete, near complete or incomplete response (see online suppl table http://links.lww.com/DCR/B835). Patient data of near complete and complete responders were reassessed in the coordinating center of the prospective study center for quality assurance reasons. Patients with a clinical incomplete response were scheduled for surgery. Patients with a complete or near complete response were restaged after 6 weeks with endoscopy (nCR) or 3 months with MRI and endoscopy (cCR).[13] In case of a (persistent) cCR patients would receive three monthly MRI and endoscopy in the first two years as part of the Watch & Wait protocol.[14]

Delayed surgery was defined as surgery after any initial conservative strategy (i.e. follow up endoscopy and/or MRI instead of TME surgery) which was decided after restaging in the MDM. Follow-up was the same for both groups. Adjuvant therapy is not (routinely) given according to the Dutch colorectal guidelines, to patients with rectal carcinoma. Therefore, the included patients did not receive adjuvant therapy.

Costs

The economic evaluation was conducted from a hospital perspective. Hospital costs were analyzed using gross costing and micro costing analyses where applicable. In both cases the hospital resource use was multiplied by the cost per unit and then calculated as mean cost per patient. Reference prices were derived from the Dutch guideline and recent literature on colorectal surgery costs in the Netherlands.[12,15,16] The most recent price cost model (2016) was used for all patients to avoid the effects of inflation and differences between models.[16] Mean gross costing on stoma reversal was based on hospital data and two international studies.[17,18] Hospital costs consisted of ambulatory contacts such as clinic visits and telephone appointments, additional examinations such as laboratory tests, CT, MRI and endoscopy and costs for admission, surgery and complications. All costs were calculated up until 30 days postoperatively and are shown in Table 2.

Statistical analysis

All time variables were calculated from the last day of chemoradiation. Date of metastases or local recurrence was defined as the first colorectal MDM where this was concluded.

Complications were registered until 30 days postoperatively. Descriptive statistics were obtained prior to analysis to identify outliers and missing/wrong data. Demographic tables were constructed for patient characteristics and operative data; Fishers' exact test were used to compare categorical variables. Linear-by-linear association was used for ordinal categorical data, such as pT stage. One way ANOVA or t-tests were used in case of a continuous dependent variable, such as distance from anus. If the assumption of a normal distribution was violated, Mann Whitney U test or Kruskal Wallis test was used. Variables with p-values <0.10 in univariate analysis were included in multivariate logistic regression analyses. Disease free survival (DFS) and overall survival (OS) at two year intervals were obtained using Kaplan Meier (log rank) survival analysis and were calculated from end of CRTx. Regrowth and persistent disease were not considered an event in survival analysis. Statistical significance was tested for using Cox proportional hazards model. DFS was defined as the absence of (re-)recurrence or metastases, OS was defined as the absence of death. Costs were compared using Mann-Whitney U Test. IBM statistics (version 23.0, Armonk, NY) was used.

RESULTS

Patient-related outcomes

Between Jan 2015 and May 2020, 622 patients with rectal cancer were treated in our hospital of which 200 patients received neo-adjuvant CRTx. Fifty three patients followed the Watch & Wait protocol at 01-06-2020 without a regrowth at this time and were therefore not eligible for inclusion. Sixteen patients died during follow-up, 9 patients had another tumor, double tumor or no adenocarcinoma, 10 patients had synchronous metastases, 3 patients had a local excision without TME, and 3 patients were lost to follow up. For the present study, 94 patients (29 delayed surgery vs 65 immediate surgery) were finally included for the analyses (Figure 1.) There was no difference in the age, sex, ASA score or occurrence of metastases (Table 1). Clinical N-stage was significantly different between immediate and delayed surgery groups, where a lower cN-stage was more common in the delayed surgery group. There was no statistically significant difference in clinical T staging or involvement of the mesorectal fascia. Mean distance of the tumor from the anal verge was significantly shorter for the delayed surgery group.

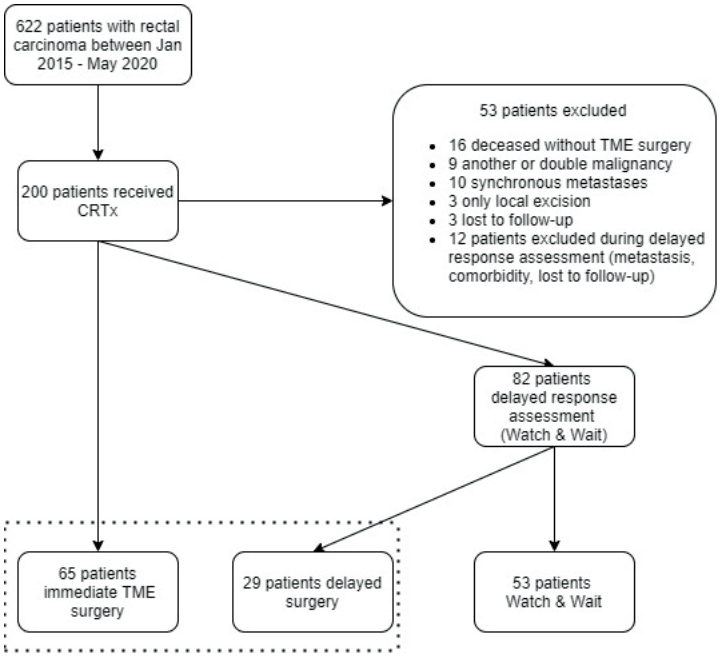


Figure 1 | Flow chart depicting process of patient inclusion.

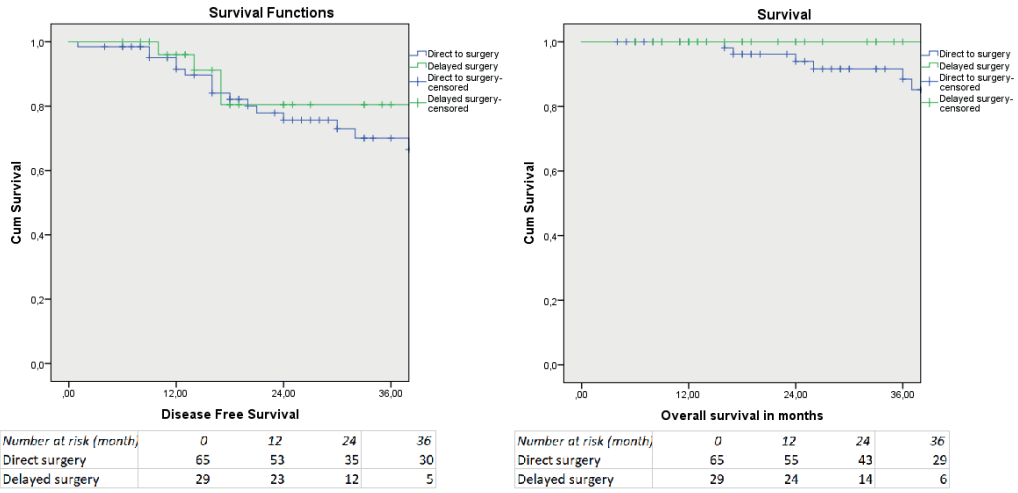
Table 1. Patient demographics for immediate vs delayed surgery.

Patient data		Immediate surgery			Delayed surgery			
		Count	%	Mean	Count	%	Mean	p
Age				66			64	0.33
Sex	M	36	55.4%		20	69.0%		0.26
	F	29	44.6%		9	31.0%		
ASAscore	1	17	26.2%		12	41.4%		0.31
	2	44	67.7%		15	51.7%		
	3	4	6.2%		2	6.9%		
Endoscopic distance from anal verge (cm)				9			6	**0.03**
Time to surgery (weeks)				16			41	**< 0.01**
cT	2	1	1.5%		1	3.4%		0.29
	3	55	84.6%		27	93.1%		
	4	9	13.8%		1	3.4%		
cN	0	2	3.1%		6	21.4%		**<0.01**
	1	18	27,7%		9	32.1%		
	2	45	69.2%		13	46.4%		
Mesorectal fascia	+	12	19.0%		5	17.9%		1.0
	-	51	81.0%		23	82.1%		

*Variables in **bold** are statistically significantly different (p < 0,05).*

Surgical outcome

There were more laparoscopic procedures in the delayed surgery group (p = 0.03), but no differences in conversion rate, free resection margins (CRM), pT stage and operating time were found (Table 2). In the delayed surgery group, a lower mean ypN stage was observed analogous to the lower cN stage (p = 0.02). There is a trend towards more APR vs LAR procedures in the delayed surgery group due to more distally located tumors, although operation type is not significantly different (p = 0.09). There is a non-significant trend towards more surgical reinterventions and readmissions in the immediate surgery group. One patient had a multivisceral resection which was classified as 'other'. Multivariate analysis showed no significant differences in morbidity between immediate and delayed surgery groups (Table 2).



Number at risk (month)	0	12	24	36
Direct surgery	65	53	35	30
Delayed surgery	29	23	12	5

Number at risk (month)	0	12	24	36
Direct surgery	65	55	43	29
Delayed surgery	29	24	14	6

Figure 2 | Kaplan Meier curve of overall survival (OS) and disease free survival (DFS) between immediate and delayed surgery groups.

Table 2 | Surgical outcomes for immediate vs delayed surgery groups.

		Immediate surgery		Delayed surgery		Univariate analysis	Multivariate analysis
		Count	Mean	Count	Mean	p-value	p-value
Type of operation	APR	20	30.8%	16	55.2%	0.09	0.60
	Hartmann	4	6.2%	0	-		
	LAR	40	61.5%	13	44,8%		
	Other	1	1,5%	0	-		
Operating time (min)			206		232	0.09	0.22
Laparoscopy	no	13	21.0%	1	3.4%	**0.03**	
	yes	49	79.0%	28	96.6%		
Conversion	no	58	93.5%	28	96.6%	0.67	
	yes	4	6.5%	1	3.4%		
Stoma	none	8	12.3%	3	10.3%	0.25	
	temporary	33	50.8%	10	34.5%		
	permanent	24	36.9%	16	55.2%		
ypT	0	11	16.9%	0	-	0.39	
	1	2	3.1%	0	-		
	2	11	16.9%	14	48.3%		
	3	38	58.5%	15	51.7%		
	4	3	4.6%	0	-		
ypN	0	34	52.3%	21	75.0%	**0.02**	0.07
	1	21	32.3%	7	25.0%		
	2	10	15.4%	0	-		
CRM	not free	3	4.6%	1	3.4%	1.0	
	free	62	95.4%	28	96.6%		
Length of stay			9		8	0.83	
Readmission	**no**	**44**	**73.3%**	**26**	**89.7%**	**0.10**	**0.13**
	yes	16	26.7%	3	10.3%		
Surgical reintervention	no	51	85.0%	28	96.6%	0.16	0.53
	yes	9	15.0%	1	3.4%		

*Bold **p values** are significant at < 0.05.*

Table 3 | shows resource use of the immediate and delayed surgery groups including mean clinic visits and telephone consults for various specialties and professionals, examinations and perioperative costs from first visit to 30 days post operation.

	Immediate surgery					Delayed surgery				
	Cost per unit	Median per patient	Total no	Total cost	Cost per pt	Median per patient	Total no	Total cost	Cost per pt	p-value
Clinic surgeon	91	2	155	14105	217.00	5	150	13650	470.69	<0.01
Clinic oncologist	91	2	143	13013	200.20	2	70	6370	219.66	
Clinic radiotherapist	50	5	310	15500	238.46	4	126	6300	217.24	<0.01
Clinic stoma nurse	35	1	120	4200	64.62	1	48	1680	57.93	
Clinic case manager	35	7	422	14770	227.23	6	165	5775	199.14	
Clinic specialist nurse	35	0	46	1610	24.77	1	105	3675	126.72	
Tel consult surgeon	63	0	11	693	10.66	0	27	1701	58.66	
Tel consult stoma nurse	12	1	145	1740	26.77	1	54	648	22.34	
Tel consult case manager	12	3	283	3396	52.25	3	163	1956	67.45	
Tel consult specialist nurse	12	0	27	324	4.98	1	23	276	9.52	
Subtotal				69351	**1067**			42031	**1449**	
Colonoscopy	415.76	2	127	52801.52	812.33	4	124	51554.24	1777.73	<0.01
CEA	12.40	1	79	979.60	15.07	3	77	954.80	32.92	<0.01
MRI	340	2	143	48620	748.00	4	113	38420.00	1324.83	<0.01
CT	135	4	237	31995	492.23	4	125	16875.00	581.90	
Chest x-ray	44.60	0	8	356.80	5.49	0	2	89.20	3.08	
Liver ultrasound	70.50	0	7	493.50	7.59	0	3	211.50	7.29	
PET	1284	0	2	2568	39.51	0	2	2568.00	88.55	
Subtotal				137814.42	**2120**			110672.74	**3816**	

	Immediate surgery					Delayed surgery				
	Cost per unit	Median per patient	Total no	Total cost	Cost per pt	Median per patient	Total no	Total cost	Cost per pt	p-value
ICU days	1186	0	2	2372	36.49	0	10	11860	408.97	
Readmission LOS (days)	476	0	98	46648	717.66	0	23	10948	377.52	
Operating time (min)	11.74	200	11975	140586.50	2162.87	240	6670	78305.80	2700.20	
Operating time local excision (min)	11.74	0	350	4109	63.22	0	315	3698.10	127.52	
Surgical reintervention (min)	11.74	0	466	5470	84.17	0	178	2089.72	72	
Stoma reversal	4800	0	26	124800	1920	0	6	28800	993.1	
Subtotal				567221.5	**8726**			246609.62	**8504**	
Total				1014732.90	**11913**			496351.64	**13769**	

Significant p-values <0.05 are given.

Resource use and costs

Table 3 shows the resource use for the immediate and the delayed surgery groups. As expected, the delayed surgery group had significantly more surgical clinic visits, laboratory tests, MRI examinations, endoscopies and pathology examinations ($p < 0.01$ for all) leading to higher mean costs per patient for clinic appointments and investigations. The immediate surgery group had a total of 511 admission days, 98 readmission days of which 58 days were spent by 4 patients, 11975 minutes of surgery, 350 minutes for a prior local procedure, 466 minutes of complication surgery and 26 stoma reversals resulting in a mean perioperative cost of €8726 per patient. The delayed surgery group had a total of 233 admission days of which 1 patient spent 10 days in ICU, 23 readmission days, 6670 minutes of surgery, 315 minutes for a prior local procedure, 178 minutes of complication surgery and 6 stoma reversals resulting in a mean perioperative cost of €8504 per patient. Ultimately, the total mean cost per patient was not significantly different; €11913 in the immediate surgery group and €13769 in the delayed surgery group ($p = 0.89$). All results are shown in Table 3.

Oncological outcome and stoma-free survival

We observed a longer mean follow-up time in the immediate surgery group. Two year DFS was 78% in the immediate surgery group and 81% in the delayed surgery group (Table 4). There were no significant differences in DFS ($p = 0.47$) and OS ($p = 0.24$) between the immediate and delayed surgery group (Figure 2). There were 87 patients alive at time of final analysis. Stoma-free rate was 53% (30/57) in the immediate surgery group vs 31% (9/29) in the delayed surgery group ($p = 0.09$). For patients with a primary anastomosis, stoma-free rate was 73% (30/41) in the immediate surgery group vs 75% (9/12) in the delayed surgery group ($p = 0.9$).

Table 4 | Survival outcomes and follow up for immediate vs delayed surgery calculated from end of CRTx.

Survival		Immediate surgery			Delayed surgery			
		Percentage	[95% CI]	Count	Percentage	[95% CI]	Count	P-value
2 year DFS		78%	[73 to 92]		81%	[57 to 93]		0.47
2 year OS		93%	[84 to 99]		100%	[-]		0.23
Stoma-free rate		53%		(30/57)	31%		(9/29)	0.09
Distant relapse rate	*No*	77%		(50/65)	86%		(25/29)	0.41
	yes	23%		(15/65)	14%		(4/29)	
Follow up (months)		31.4			24.0			**0.045**

*P-values in **bold** are significant at p <0.05*

DISCUSSION

Delayed TME surgery for regrowth in a W&W program or for persistent residual disease after a repeated assessment strategy is safe and is not unfavorable for those patients who require surgery at a later stage. The extra costs related to delayed surgery are negligible, especially when considering the real complete responders who will avoid surgery. Although the present study is underpowered to show subtle differences, there is nothing to suggest a detrimental oncological outcome of delayed surgery.

There is some concern that patients who receive delayed rectal cancer surgery after CRT are exposed to an increased morbidity risk due to more established radiation fibrosis.[10,19] The literature on this subject does not report an increase in morbidity comparing 6 up to 14 week intervals.[20–24] However, this might not incorporate the effects of late radiation fibrosis, as the development of radiation induced fibrosis can develop after months.[25–28] Nasir et al. included 23 patients who underwent delayed surgery a mean 10 months later than 46 patients who were immediately operated after CRTx for rectal carcinoma and showed no differences in morbidity.[29]

In the present study, the delayed group undergoing TME surgery a mean 25 weeks later than the immediate group showed no significant differences in complications or any other clinical outcome parameter. In fact, we even found a non-significant trend towards less readmissions and surgical reinterventions in the delayed surgery group. These results support earlier findings that a prolonged interval between CRT and surgery does not predispose to a higher morbidity rate.

Regarding the oncological outcome of delayed surgery, literature suggests that regrowths are often salvageable with a good oncological outcome. In a series of 250 patients, Habr-Gama et al. showed no difference in survival of a subset of 23 patients receiving delayed surgery for a regrowth or misdiagnosed cCR.[30] In a series of 89 patients with regrowths from the Dutch and Portuguese prospective WW cohorts, an excellent 2-year local recurrence-free rate of 97% after treatment of the regrowth was demonstrated.[31] Our dataset representing common practice in the Netherlands included 27 cT3 tumors in the delayed surgery group and showed no difference in OS or DFS compared to immediate surgery. Survival analyses started from end of CRTx, meaning that the delayed surgery group had a relatively shorter postoperative follow-up compared to the immediate surgery group. Our data underlines that oncological outcome is not compromised by delaying TME surgery, although our sample size is small. However, there is a small group of patients who might not be salvageable due to local irresectability, comorbidity but also metastases.[32] The risk of metastases while avoiding surgery after cCR is a worry for many clinicians. Is there an increased risk for distant relapse that would have been prevented by immediate surgery? Our study was not designed to answer this question, but 7.3% (6/82) of patients in our delayed surgery group developed metastases. It is worth mentioning that almost all (5/6) patients with systemic recurrence had developed a regrowth, all of which within < 12 months. Several studies have confirmed that distant relapse is often accompanied by regrowth.[7,33]

One could argue that these early regrowths and metastases could possibly have been prevented by immediate surgery. Two reviews found a distant relapse rate of 8% in 5 years

and 6.8% in 3 years in patients with a cCR, which is comparable to the reported 8.7% in 5 years found in over 1200 patients with a pCR suggesting that risk of metastasis could be more related to tumour biology rather than the omission of immediate surgery.[14,33,34] It should be noted however, that >60% of pCR patients included in this review had received adjuvant chemotherapy. Adjuvant chemotherapy after cCR (instead of immediate surgery) to increase the likelihood of sustained cCR and distant control is still a matter of debate and larger numbers and longer follow-up is needed.[7]

Secondary to the promise of organ preservation, a WW strategy can be cost-effective compared to TME surgery.[11] Obviously, much of the cost reduction is made by avoiding surgery which outweighs the additional use of other hospital resources such as clinic visits and additional examinations.[3] We found a mean perioperative hospital cost of approx. €8700. This figure is lower than the previously calculated costs of €11.500 by Hupkens et al and €12.740 by van der Linden et al in the same healthcare system.[12,15] This is due to a lower mean hospital stay of 8 vs 13 days (€3824 vs €6157) in our study compared to Hupkens et al. Similarly, van der Linden et al also observed a higher mean cost for admission (€6692) compared to the present study. This could very well be the result of the implementation of enhanced recovery programs in more recent years.[35] Finally, Hupkens et al. found a €10.396 reduction in hospital costs from diagnosis to two years follow up comparing standard treatment to a WW strategy.[11,12] In our analysis, the cost effectiveness of a WW strategy from a hospital perspective was lost when patients require delayed TME surgery. On the other hand, the extra costs of repeated delayed response assessment in patients with a regrowth (€1856) is minimal compared to the mean perioperative costs (€8504).

For our 29 patients who underwent delayed surgery, 53 patients had a sustained cCR and remain in a WW protocol. This means a possible perioperative cost saving of €450.712 or €8504 per patient, not taking costs for further response assessment into account. These findings support the conclusion of Hupkens et al, showing that a delayed response assessment strategy is overall cost effective.

The main limitations of the present study are relatively small numbers, increasing the chance of a type 2 error of not detecting subtle differences and short follow up time of 24-31 months from chemoradiotherapy, prohibiting firm conclusions on long-term oncological outcome data. The immediate surgery group had a longer follow up time than the delayed surgery group, because of the more recent increase of patients who participate in the WW protocol. Furthermore, we did not include costs outside of the hospital and beyond 30 days postoperatively. Additional hospital costs after 30 days and costs on society level such as leave from work were therefore not included. However, notorious hospital cost influencing factors such as laparoscopic procedures and complications would have been in favour of the delayed surgery group.[36,37] The findings of this study reveal the current challenge of a delayed surgery strategy, which lies in the appropriate selection of patients. Future research should focus on better predicting a sustained complete response to neo-adjuvant treatment, so that clinical parameters can optimally predict pCR.[38–41]

CONCLUSION

Delayed TME for regrowth in a W&W program or for persistent residual disease after a repeated assessment is not associated with an increased risk of postoperative morbidity or a significant rise in costs compared to immediate TME surgery. There also appears to be no evident compromise in oncological outcome. Repeated response assessment in patients with a near complete clinical response after CRTx is a useful approach to identify more patients who can benefit from a Watch & Wait strategy.

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CHAPTER 3

Role of Local Excision for Suspected Regrowth in a Watch and Wait Strategy for Rectal Cancer

Barbara M. Geubels, **Vincent M. Meyer**[*], Henderik L. van Westreenen, Geerard L. Beets, Brechtje A. Grotenhuis[*] and on behalf of the Dutch Watch and Wait Consortium[‡]

[*]*shared first author*
[‡]*See acknowledgements for members of the Dutch Watch and Wait consortium*

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SIMPLE SUMMARY

Rectal cancer patients with a clinical complete response to neoadjuvant treatment are eligible for Watch and Wait as an alternative to total mesorectal excision. However, in patients with local regrowth, major surgery is still the standard of care. The present study evaluates the role of local excision for suspected local regrowth in a large Watch and Wait cohort, in terms of long-term outcomes. This study shows excellent overall survival and a good organ preservation rate. Patients who developed locoregional recurrence after initial local excision for regrowth were all successfully treated with salvage surgery. This study shows that local excision can provide maintenance of organ preservation without an obvious compromise in surgical or oncological safety. Local excision for suspected regrowth in patients following Watch and Wait can be a safe alternative for total mesorectal excision in selected patients with a strong wish to preserve their rectum.

ABSTRACT

Rectal cancer patients with a clinical complete response to neoadjuvant (chemo)radiation are eligible for Watch and Wait (W&W). For local regrowth, total mesorectal excision (TME) is considered the standard of care. This study evaluated local excision (LE) for suspected local regrowth. From 591 patients prospectively entered into a national W&W registry, 77 patients with LE for regrowth were included. Outcomes analyzed included histopathologic findings, locoregional recurrence, long-term organ preservation, and colostomy-free and overall survival. In total, 27/77 patients underwent early LE (<6 months after neoadjuvant radiotherapy) and 50/77 underwent late LE (≥6 months). Median follow-up was 53 (39–69) months. In 28/77 patients the LE specimen was histopathologically classified as ypT0 (including 9 adenomas); 11/77 were ypT1, and 38/77 were ypT2–3. After LE, 13/77 patients with ypT2–3 and/or irradical resection underwent completion TME. Subsequently, 14/64 patients without completion TME developed locoregional recurrence, and were successfully treated with salvage TME. Another 8/77 patients developed distant metastases. At 5 years, overall organ preservation was 63%, colostomy-free survival was 68%, and overall survival was 96%. There were no differences in outcomes between early or late LE. In W&W for rectal cancer, LE can be considered as an alternative to TME for suspected regrowth in selected patients who wish to preserve their rectum or avoid colostomy in distal rectal cancer.

Keywords

rectal cancer; Watch and Wait; local regrowth; local excision; oncological outcome; organ preservation

INTRODUCTION

In recent years, non-operative treatment strategies in excellent responders to neoadjuvant therapy have gained popularity because of the improved functional outcome and quality of life. Rectal cancer patients with a clinical complete response at restaging after neoadjuvant therapy can be safely monitored in a "Watch and Wait" (W&W) protocol.[1,2]

Most series report a local regrowth rate of 20–30% but, reassuringly, these patients are amenable to a delayed total mesorectal excision (TME) without any obvious compromise in oncological outcomes and surgical safety.[3–6] With the goal in mind of obtaining better functional results and continuing an organ-preserving approach, the question is whether small luminal regrowths can also be treated with a transanal local excision (LE).

LE has been part of organ preservation in certain strategies where in relatively early rectal tumors the scar or small remnant after chemoradiation has been removed as a planned procedure.[4,7–10] With this strategy, preservation of the rectum can be ensured in a high number of cases without compromising locoregional control.[11,12] LE can also be performed more selectively for tumors that, while responding well, do not show the typical picture of a clinical complete response (also labeled as near-complete response). Yet another approach in organ preservation is to perform LE when a regrowth occurs, or is suspected, during follow-up in the W&W strategy.[10] Tumor regrowth is reappearance of neoplasia at the site of the primary tumor after a clinical complete response to neoadjuvant therapy in a W&W program, where TME has been omitted—in contrast to the definition of locally recurrent rectal cancer, which occurs after TME, and is much more difficult to treat, with a more reserved prognosis. In the use of LE for regrowth in a W&W approach, there is nevertheless some concern that there may be more extended residual tumor through the bowel wall and in the mesorectal lymph nodes—especially in patients who originally had a more advanced tumor. LE would then expose patients to undertreatment, with risks of recurrence.[13–16]

To date, two studies have reported on the oncological outcomes of LE for regrowth.[6,17]

The aim of the present study was to evaluate the outcomes of patients who underwent LE for suspected regrowth in a large W&W cohort in the Netherlands.

MATERIALS AND METHODS

Patient Data

Patients with rectal cancer who followed a W&W strategy after neoadjuvant (chemo) radiation between 2004 and 2017 were prospectively included in a local study from the Maastricht University Medical Center, approved by the local institutional review board and registered on ClinicalTrials.gov since 2009 (NCT00939666 and NTC02278653). W&W patients from 2017 onwards were prospectively included in the national multicenter registry study "Wait-and-see" Policy for Complete Responders After Chemoradiotherapy for Rectal Cancer (ClinicalTrials.gov NCT03426397), coordinated by the Netherlands Cancer Institute in Amsterdam. For quality assurance purposes, the response evaluation data from the multicenter study from

2017 onwards were reassessed by the coordinating center, all participating centers were site-visited and teaching sessions were organized. Written informed consent was obtained from all patients.

Neoadjuvant Treatment, Selection, and Follow-Up in the W&W Program

Patients were treated with long-course chemoradiotherapy (28 fractions of 1.8 Gy or 25 fractions of 2.0 Gy) with twice-daily bolus capecitabine 825 mg/m2, or with short-course radiotherapy (5 fractions of 5 Gy) followed by a prolonged waiting interval. Restaging was performed with digital rectal examination (DRE), endoscopy, and MRI 8–12 weeks after the radiotherapy. Patients with a clinical complete response entered the W&W protocol.

Patients with a very good response and no signs of residual tumor but not the typical image of a complete response—such as a small superficial ulceration—could also enter the W&W protocol under the label near-complete response. Patients with persistent near-complete response at repeated assessment were recommended for TME, but were also given the option of LE if technically feasible. Standard follow-up consisted of computed tomography scan, colonoscopy, and carcinoembryonic antigen measurements according to national guidelines, for 5 years. The additional follow-up in the W&W program consisted of DRE, endoscopy, and MRI including diffusion-weighted imaging every 3 months for the first 2 years, and 6-monthly thereafter for up to 5 years.

Diagnosis and Treatment of Regrowth

Regrowth during follow-up in the W&W program was preferably proven by biopsy, but sometimes there were only suspicious findings on endoscopy or MRI. Patients were offered TME as the standard treatment option, and LE by performing transanal endoscopic microsurgery (TEM) or transanal minimally invasive surgery (TAMIS) if the local regrowth was small and without signs of involved lymph nodes on MRI (or as a diagnostic procedure when the regrowth was not proven). Ultimately, the choice between TME or LE depended on the patient's preference, comorbidities, and the advice of the multidisciplinary team.

When patients underwent LE for regrowth, and the histological examination of the resection specimen showed ypT0 or ypT1 with free resection margins (>1 mm), the patients continued follow-up in the W&W protocol. Completion TME was advised when the resection specimen showed ypT2–3 or an irradical resection (i.e., microscopic margin involvement with the tumor either laterally or at a deep resection surface (R1), or a too-fragmented resection specimen).

Outcomes

Reported outcomes were histopathologic findings after LE, locoregional-recurrence free survival after LE, overall survival, organ preservation rate, colostomy-free survival and 90-day morbidity after LE, completion TME, and salvage TME. Locoregional recurrence after LE was specified as any luminal or (nodal) mesorectal recurrent disease within the pelvis. Subgroup analyses were performed for "early" and "late" LE, with a cutoff at 6 months after

the last radiation, to capture any differences between persistent disease (i.e., near-complete response that never evolved into a clear clinical complete response) and regrowths after an initial clinical complete response.

Data Analysis

Statistical analysis was performed with IBM SPSS statistics version 27. Descriptive statistics were provided for baseline and treatment variables, as well as outcome measures. Follow-up time was calculated from primary MRI until the date of the last follow-up moment for all outcome measures, except for the locoregional-recurrence-free interval, which was calculated from LE until locoregional recurrence or death. Kaplan–Meier survival methods were used for survival analysis.

RESULTS

Patient Characteristics

Between 2004 and 2019, 591 rectal cancer patients were prospectively registered in the W&W registry, with a minimum follow-up of two years (Figure 1); 68% of the patients were male, and their median age was 65 years. Most patients were diagnosed with cT3–4 rectal cancer (81%) and cN+ disease (72%). The majority of the patients (92%) were treated with neoadjuvant chemoradiation. The rectal tumor was located in the distal rectum (i.e., <5 cm from the anal verge) in 65% of patients.

During follow-up, 166 patients underwent surgical treatment for a suspected regrowth, of whom 77 patients underwent LE and were included in the present study (Figure 1). Baseline characteristics are shown in Table 1. The median time (IQR) between the end of neoadjuvant treatment and first restaging was 8 (7–11) weeks. A clinical complete response was seen at that time in 26 patients (34%), while 51 patients (66%) were considered as having a clinical near-complete response.

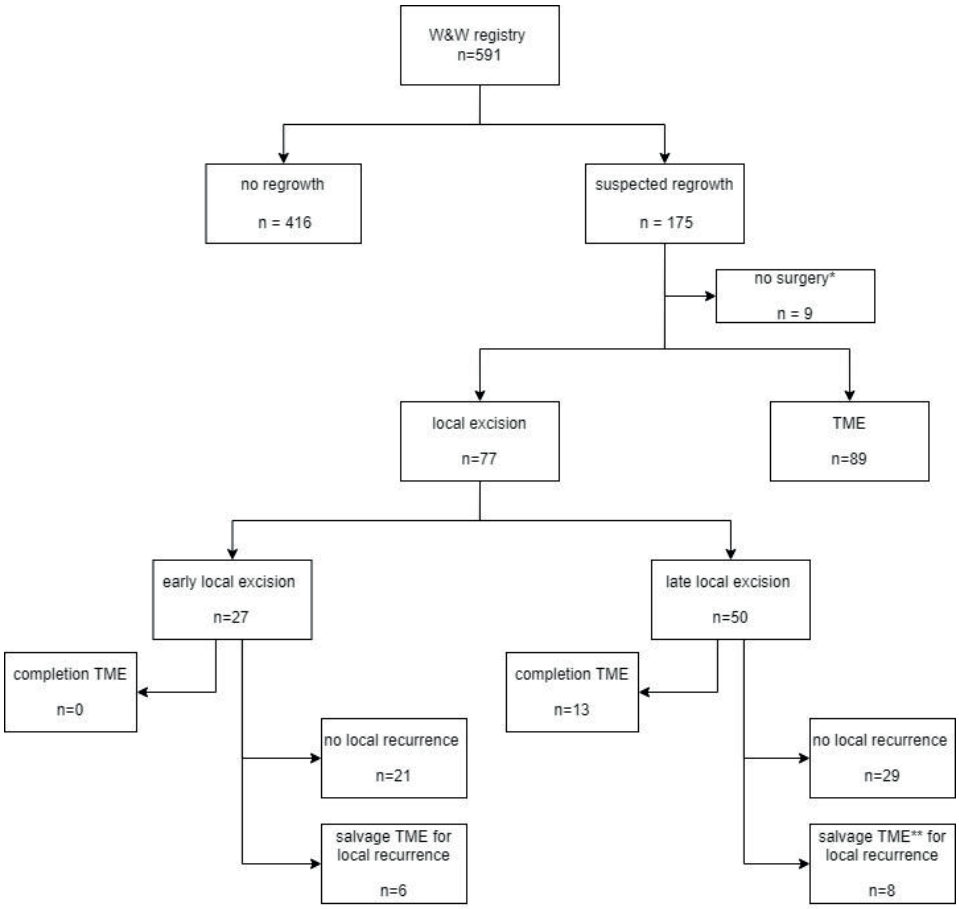

Figure 1 | Flowchart depicting patient flow.

*Abbreviations: W&W = Watch and Wait; TME = total mesorectal excision; * due to widespread metastases, frailty or patient preferences; ** n = 1 salvage TME after second local excision.*

Table 1 | Baseline characteristics of n = 77 patients who underwent local excision for suspected regrowth within the W&W cohort.

	n = 77
Age, median (range), years	66 (43 – 87)
Sex, n (%)	
Male	57 (74)
Female	20 (26)
Clinical T stage, n (%)	
T1	6 (8)
T2	19 (25)
T3	47 (61)
T4	5 (7)
Clinical N stage, n (%)	
N0	33 (43)
N1	25 (33)
N2	19 (25)
Distance anal verge, mean (SD), cm	2.8 (2.8)
<5cm, n (%)	59 (77)
≥5cm, n (%)	18 (23)
Neoadjuvant therapy, n (%)	
- chemoradiotherapy	66 (86)
- short-course radiotherapy + interval	11 (14)

The median time (IQR) between the end of (chemo)radiation and LE was 7 (5–11)months. LE was performed within 6 months in 27/77 (35%) patients, and after 6 months in 50/77 (65%) patients. There were 23/27 (85%) patients with a near-complete response at first restaging in the early LE group, in contrast to 28/50 (56%) patients in the late LE group. 3.2. Histology after LE Histological results are shown in Table 2. Overall, in 28/77 (36%) patients the LE specimen was histologically classified as ypT0, with adenoma in 9, fibrosis or inflammation in 8, and nonspecific findings in 11. In 20 of these 28 ypT0 cases, an endoscopic biopsy had been performed preoperatively, of which 8 were suspected for malignancy.

Table 2 | Histological results after early (<6months after last radiation) and late (>6months) local excision.

	early LE n=27	late LE n=50
ypT stage, n (%)		
ypT0	15 (56)	13 (26)
ypT1	4 (15)	7 (14)
ypT2	7 (26)	25 (50)
ypT3	1 (4)	5 (10)
Radical resection, n (%)	27 (100)	46 (92)

Abbreviations: LE = local excision

Overall, the LE specimens revealed ypT1 tumors in 11 (14%) patients, ypT2 in 32 (42%) patients, and ypT3 in 6 (8%) patients. In 37 of the 49 patients with ypT1–3, an endoscopic biopsy had been performed prior to the LE, of which 32 were suspected for malignancy.
The margins were clear of tumor cells in 73/77 (95%) patients. One patient had tumor involvement at the deep margin, and another at the deep and lateral margin. In two patients, the resection specimen was too fragmented and not possible to reconstruct. Therefore, we concluded that in four patients a radical resection of the lesion was not achieved.
In the early LE group there were relatively more ypT0 cases than in the late group: 15/27 (56%) versus 13/50 (26%). In the early LE group, no completion TME was performed, including the 8 patients with ypT2 or ypT3 tumors who declined completion surgery. In the late LE group, 13 patients (1 patient with a ypT1 tumor and irradical resection, 8 patients with ypT2 tumors, and 4 patients with ypT3 tumors) underwent completion TME.

Long-Term Outcomes
The median follow-up time (IQR) was 53 (39–69) months. Three patients died during follow-up: one patient from unrelated disease and two patients from metastatic disease. The 2-year and 5-year overall survival was 99% and 96%, respectively. Overall, 2-year and 5-year locoregional-recurrence-free survival after LE was 85% and 71%, respectively. Fifteen out of all seventy-seven patients (19%) developed a locoregional recurrence. Of 49/77 patients with actual regrowth (ypT1–3), 11 (22%) patients experienced locoregional recurrence, with 2-year and 5-year locoregional-recurrence-free survival after LE of 74% and 62%, respectively. As shown in Table 3, 14 out of 64 (22%) patients who did not undergo completion TME developed locoregional recurrence: 10 luminal regrowths, 3 nodal regrowths, and 1 nodal regrowth combined with combined liver metastases. All of these 14 patients underwent successful salvage TME with a radical resection. Of the 13 patients who underwent completion TME, 1 patient developed an iliac lymph node recurrence and 2 patients developed distant metastases. After TME surgery, the median follow-up time (IQR) was 28 months (19–42).

Table 3 | Oncological outcomes and organ preservation subdivided for patients with and without completion TME after local excision.

	no completion TME n = 64	**completion TME n = 13***
Local recurrence only, n (%)	13 (20%)	*na*
Luminal, n	10	
Nodal, n	3	
Local + systemic recurrence, n (%)	1 (2%)	*na*
Systemic recurrence only, n (%)	5 (8%)	2 (15%)
Salvage TME, n (%)	14 (22%)	*na*
Local recurrence after TME, n (%)	0	1 (8%)
Colostomy rate, n (%)	10 (13%)	11 (85%)
Alive	62 (97%)	12 (92%)

*Abbreviations: TME = total mesorectal excision; *n = 1 patient with ypT1 and irradical resection, n = 12 patients with ypT2–3; na = not available.*

The remaining 50 patients who did not undergo completion or salvage TME continued follow-up in the W&W protocol, and 5 patients developed distant metastases at a later stage. There were no significant differences in locoregional recurrence between the early and late LE groups (Figure 2).

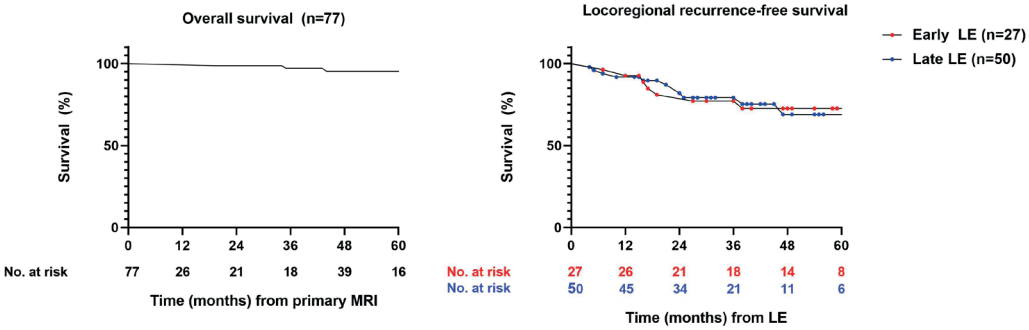

Figure 2 | Kaplan–Meier curves for (a) overall survival and (b) locoregional-recurrence-free survival for the early and late local excision groups.

The overall organ preservation rate at 2 and 5 years was 79% and 63%, respectively. Colostomy-free survival was 81% at 2 years and 68% at 5 years.

Complications after LE and TME Surgery

After LE, 6/77 (8%) patients had Clavien–Dindo grade 2 or higher complications. Of these, one patient was admitted to the intensive care unit secondary to heart failure, and five had surgical complications: two postoperative bleedings, two wound dehiscences, and one patient with an abscess. No interventions were required.

After completion TME, 3/13 (23%) patients experienced a Clavien–Dindo grade 2 or higher complication: one pneumonia, one prolonged ileus, and one anastomotic leakage requiring surgery.

After salvage TME, 3/14 (21%) patients experienced a complication classified as Clavien–Dindo > 2. One patient developed pneumonia treated with intravenous antibiotics, an abscess was treated with antibiotics and, finally, one patient developed an anastomotic leak, for which a reoperation was performed.

DISCUSSION

The aim of the present study was to report the outcomes of LE for proven or suspected regrowths in a W&W approach, with the goal of maintaining organ preservation. The overall 5-year survival of 96% in this selected patient group was good. A locoregional recurrence occurred in 22% of the large group of patients who did not undergo completion TME, and in 8% of the small group of patients who underwent completion TME. All local recurrences after LE were salvaged with TME surgery without further recurrence. With a 68% colostomy-free survival and 63% organ preservation rate at 5 years, LE can provide maintained organ preservation in a substantial number of patients with a proven or suspected regrowth, without any obvious compromise in surgical or oncological safety in this selected group of patients following W&W.

Many centers favor TME resection as locoregional treatment for the 30% of patients with a regrowth, because LE may be considered oncologically suboptimal for a tumor that was T3 or N+ on baseline imaging. There are two reports on the use of LE for regrowths in a W&W protocol. In the series reported by Fernandez et al., 32% of regrowths were treated with LE, with a local recurrence rate of 14%. In the series reported by Van der Sande et al., 30% of regrowths were treated with LE, with a local recurrence rate of 8%.[6,17] The present study showed a higher local recurrence rate of 19%, most likely related to the more advanced stage at baseline staging and our more liberal use of LE, as 44% of patients with regrowth underwent LE (Figure 1). Ultimately, the most important oncological question remains whether a local recurrence after LE will lead to uncontrolled locoregional disease. Both other studies reported that all local recurrences were salvaged with TME. In the present study, all local recurrences after LE underwent radical resection after TME surgery, with no further local recurrence in the follow-up. Finally, the overall long-term outcomes of the present cohort were very good, and compare favorably to series that report on the outcomes of immediate TME surgery as treatment for regrowths in a W&W approach.[5,16]

The present study also included LE for lesions that were suspicious, but not proven to be malignant. In some patients with a near-complete response, remnant lesions may not disappear with further follow-up. A negative biopsy does not rule out residual tumor, creating a diagnostic dilemma.[18] In other patients, adenomatous lesions can appear in the scar during follow-up, with a biopsy showing low- or high-grade dysplasia, but no invasive cancer. Again, this creates the same diagnostic dilemma: should we wait longer, or should we remove the lesion? A diagnostic LE can provide a definitive answer, while also providing the chance of being therapeutic in case of a small residual tumor. In the present series, diagnostic LE in terms of ypT0 histological outcomes was much more common in the first 6 months of follow-up.

Some surgeons favor routine LE of the scar after chemoradiation, with the goal of removing any potential small tumor remnants and avoiding regrowths. Studies on this strategy generally report low local recurrence rates, such as the reports by d'Alimonte et al. and Bushati et al., who both reported an 8% local recurrence rate.[11,12] The downside of conducting routine LE is that some reports have shown a higher complication rate compared to LE without preceding radiotherapy, although in the present study only 8% of patients had Clavien–Dindo > 2 complications. Additionally, worse functional outcomes of LE after radiotherapy have been reported.[19–23] As the majority of patients with a clinical complete or near-complete response have no residual tumor, they will gain no benefit from routine LE, while increasing their chances of anorectal dysfunction. In a recent review on the role of LE for organ preservation after radiotherapy, Perez et al. noted that most surgeons have moved away from routine LE, and made a case for much more selective use.[24]

This study has limitations. Some of the concepts and practices of W&W evolved during the 15-year study period. Initially, only patients with a typical clinical complete response were included, and the concept of near-complete response developing into a complete response with further observation gradually led to more inclusion of near-complete responders. Likewise, the use of LE for suspected or proven regrowths gradually increased over time, as a result of a favorable experience in highly selected patients in the early study period.[6] Therefore, only a small group of patients with LE for suspected regrowth completed the 5-year follow-up.

In addition, this is a database-based registry study with variability between participating centers. The indication for LE was at the discretion of the local colorectal team, and was not well documented. It was not possible to reconstruct the exact considerations in the 44% of patients in whom it was decided to perform LE rather than TME. In general, the lesion had to be small, with no evidence of mesorectal lymph nodes or deposits, preferably not located anteriorly (i.e., close to the prostate or vaginal wall) and, provided LE was technically feasible, the patient had to express a strong wish for organ preservation.

Finally, in a W&W strategy, LE can be an alternative to TME surgery for a suspected or proven regrowth in patients with a strong wish to preserve their rectum or avoid a colostomy in distal rectal cancer. However, an important issue regarding the applicability of the results of this study in daily clinical practice is that patients in the present cohort were generally treated by dedicated colorectal teams and in highly experienced centers for W&W.

Although in the present series all local recurrences after LE could successfully be salvaged with TME without further local recurrence, caution is required given the limitations of the current study. Shared decision making, balancing the functional benefit of LE and organ preservation against the (small) potential oncological risk, is essential.

CONCLUSIONS

In conclusion, LE for suspected regrowth can provide maintained organ preservation in a substantial number of patients following W&W, without any obvious compromise in surgical or oncological safety. In a W&W program for rectal cancer, LE can be considered as an alternative to TME for suspected regrowth in selected patients who wish to preserve their rectum or avoid a colostomy in distal rectal cancer.

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CHAPTER 4

Prognostic importance of lymph node count and ratio in rectal cancer after neoadjuvant chemoradiotherapy: Results from a cross-sectional study

Robin Detering MD, PhD, **Vincent M. Meyer MD**[*], Wernard A.A. Borstlap MD, PhD, Regina G.H. Beets-Tan MD, PhD, Corrie A.M. Marijnen MD, PhD, Roel Hompes MD, PhD, Pieter J. Tanis MD, PhD, Henderik L. van Westreenen MD, PhD, the Dutch Snapshot Research Group
[*]*shared first author*

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ABSTRACT

Background
The aim of this study was to determine the prognostic value of lymph node count (LNC) and lymph node ratio (LNR) in rectal cancer after neoadjuvant chemoradiotherapy (CRT).

Methods
Patients who underwent neoadjuvant CRT and total mesorectal excision (TME) for Stage I–III rectal cancer were selected from a cross-sectional study including 71 Dutch centres. Primary outcome parameters were disease-free survival (DFS) and overall survival (OS). Prognostic significance of LNC and LNR (cut-off values 0.15, 0.20, 0.30) was tested for different (sub) groups.

Results
From 2095 registered patients, 458 were included, of which 240 patients with LNC < 12 and 218 patients with LNC ≥ 12. LNC was not significantly associated with DFS ($p = 0.35$) and OS ($p = 0.59$). In univariable analysis, LNR was significantly associated with DFS and OS in the whole cohort and LNC subgroups, but not in multivariable analysis.

Conclusions
LNC was not associated with long-term oncological outcome in rectal cancer patients treated with CRT, nor was LNR when corrected for N-stage.
However, LNR might be used to identify subgroups of node-positive patients with a favourable outcome.

Keywords
chemoradiotherapy, disease-free survival, lymph nodes, rectal cancer, survival

INTRODUCTION

Positive nodal stage is an important prognosticator in colorectal cancer and total lymph node count (LNC) has also been shown to be independently associated with survival.[1,2] The American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UIAC) advise a minimum retrieval of 12 lymph nodes, although the exact cut-off value has been debated.[3] A minimal LNC potentially prevents understaging as a low LNC might not adequately represent lymph node status.

LNC has been considered to be a proxy of adequacy of both surgical lymphadenectomy and pathological examination of the specimen. However, LNC varies depending on factors like age, tumour location, tumour stage, and lymph node size.[4–6] Furthermore, LNC decreases after neoadjuvant chemoradiotherapy (CRT) for which reason LNC might not be an adequate parameter for staging in rectal cancer after CRT.[7,8] Only 20% of cases who receive neoadjuvant therapy yield a LNC ≥ 12.[9,10] In fact, several studies have shown that a low LNC could reflect a good response to neoadjuvant treatment.[11–13] Whether LNC correlates with long-term oncological outcomes in rectal cancer is still an area of controversy, especially in the setting of neoadjuvant therapy.

Positive lymph node status (N+) and LNC can be combined into the lymph node ratio (LNR), which is defined as the total number of positive lymph nodes divided by the LNC. It has been shown to be an independent predictor of survival in gastric, pancreatic, and colon cancer, as well as in rectal cancer patients.[14,15] However, the available evidence on LNR as prognostic factor in rectal cancer after CRT is limited. Furthermore, the LNR has been used within several subpopulations of rectal cancer depending on neo-adjuvant treatment, N-stage, and LNC, as well as with different cut-off values.

Therefore, the aim of this multicentre cross-sectional study was to evaluate the value of LNC and LNR as prognostic factors for disease-free survival (DFS) and overall survival (OS) after CRT followed by total mesorectal excision (TME) surgery for rectal cancer, both in the overall cohort and specific subgroups.

PATIENTS AND METHODS

This multicentre cross-sectional study conducted by the Dutch Snapshot Research Group (DSRG) was performed in 71 out of 94 hospitals in the Netherlands in 2015. Data were retrospectively collected in the participating Dutch hospitals of all surgically treated rectal cancer patients in 2011, which were available from the mandatory Dutch ColoRectal Audit (DCRA).[16] Additional data on diagnostic and treatment characteristics, and short- and long-term surgical and oncological outcomes were retrospectively added to the DCRA data set. Detailed information of this Snapshot study design has been published previously.[17]

Patients

All patients with locally advanced rectal carcinoma who underwent CRT followed by TME surgery between January 1, 2011 and December 31, 2011 were selected. Based upon the national guidelines, locally advanced rectal cancer was defined as: cT4 tumor, and/or involvement of the mesorectal fascia and/or more than three positive lymph nodes on magnetic resonance imaging (N2). Detailed data on CRT schedule were not registered, but CRT

schedules consisted either of 28 fractions of 1.8Gy or 25 fractions of 2Gy, with concomitant capecitabine according to the Dutch colorectal cancer guideline. For the purpose of this study, patients with synchronous metastases, and patients who received adjuvant chemotherapy were excluded. Adjuvant chemotherapy is not recommended in the Dutch colorectal cancer guideline for any patient with resected Stage I–III rectal cancer. Therefore, the minority of patients who did receive adjuvant chemotherapy was excluded to increase homogeneity of the cohort.

Data extraction

The following data were extracted: patient- (gender, age, BMI, ASA-score), and diagnostic characteristics including distance to the anorectal junction (ARJ), and clinical tumour- and nodal stage. The following procedural characteristics were extracted: multivisceral resection, approach, procedure and interval between CRT and surgery (<14 vs. ≥14 weeks; cut-off based on a previous study).[17]

Pathological outcomes included histological outcomes, tumour- and nodal stage, and circumferential resection margin (CRM) involvement (tumour-free resection margin ≤1 mm). For determining longterm outcomes, date of any disease recurrence, date of death from any cause, and last date of follow-up were extracted.

Outcome parameters and patient subgroups

Primary outcome parameters were 3-year DFS and OS. Patients were divided in several subgroups for the purpose of this study. Based on the generally accepted LNC cut-off of 12, patients were divided into low LNC (<12 examined lymph nodes) and high LNC (≥ 12 examined lymph nodes). For analysis of the LNR, patients were divided into low LNR and high LNR groups. Optimal cut-off values for LNR have been determined using different methods varying from ROC curves, mean or median values, atypical selections and maximal $\chi 2$ methods. We based our study on a selection of three frequently reported cut-off levels of 0.15, 0.20, and 0.30.18–22 Within the node-positive population, additional subgroups based on ypN1 and ypN2 were defined.

Statistical analysis

Categorical and dichotomous outcomes were expressed as frequencies and percentages and continuous outcomes were expressed as median with interquartile range (IQR). The prognostic significance of LNC was tested for the whole cohort. LNR was analysed for the whole cohort, as well as for the following subgroups: ypN1-2, ypN1, ypN2, LNC < 12, and LNC ≥ 12. Kaplan–Meier analysis was used to determine the DFS and OS probabilities. The log-rank test was used for comparison of survival outcomes between predefined subgroups of patients based on LNC and LNR. Univariable and multivariable Cox regression analysis was performed to identify predictors for DFS and OS in the whole population and within distinct subgroups. Variables with $p < 0.10$ in univariable analyses were used in the multivariable model. $p < 0.05$ were considered statistically significant. The results were reported in hazard ratios (HRs) with 95% confidence intervals (CIs). Statistical analyses were performed in PASW Statistics, version 24 (SPSS Inc.).

RESULTS

Of 2095 registered patients who underwent TME surgery in 2011, a total of 458 rectal cancer patients who received CRT and TME were included for the present analyses (Figure 1). Table 1 shows the pathological and long-term oncologic outcomes of the included patients. The majority were staged as ypT3, and the overall CRM + rate was 10.3%. A total number of 5349 lymph nodes were retrieved, of which 488 were tumour-positive. A total of 2698 lymph nodes were retrieved after a short CRT-surgery interval (<14 weeks). In 305 of the 458 patients, only tumour negative nodes were found (Figure S1). Dividing patients based on median LNC (<12 and ≥12 examined lymph nodes) resulted in 240 (52.4%) patients in the low LNC group and 218 (47.6%) patients in the high LNC group. The median long-term follow-up was 43 months [IQR: 34–47]. Of the total group, 3-year DFS was 72.3% and 3-year OS was 84.9%.

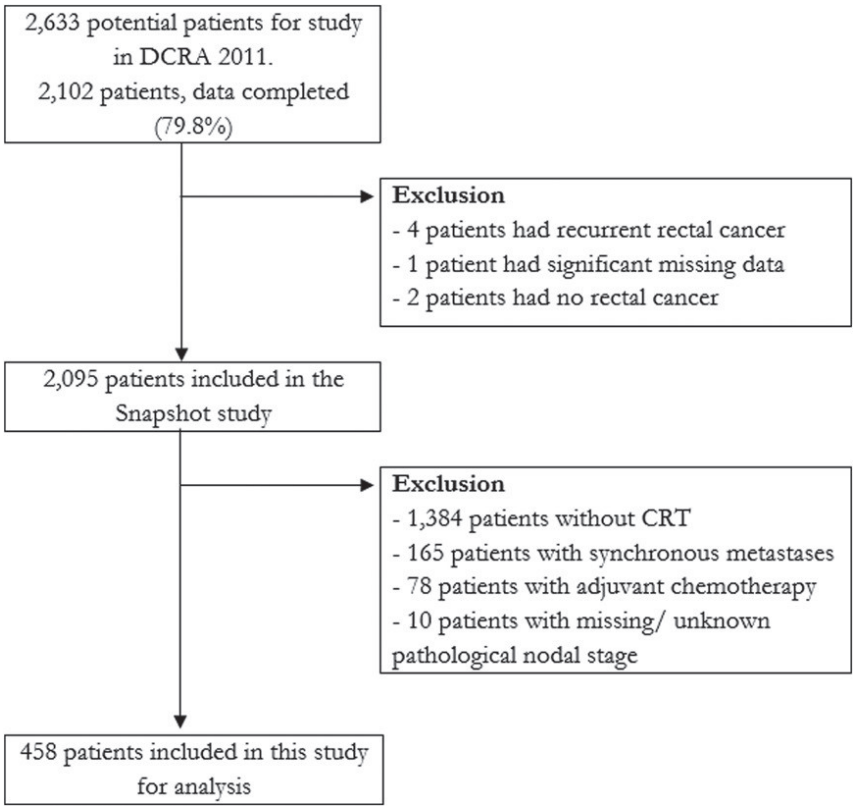


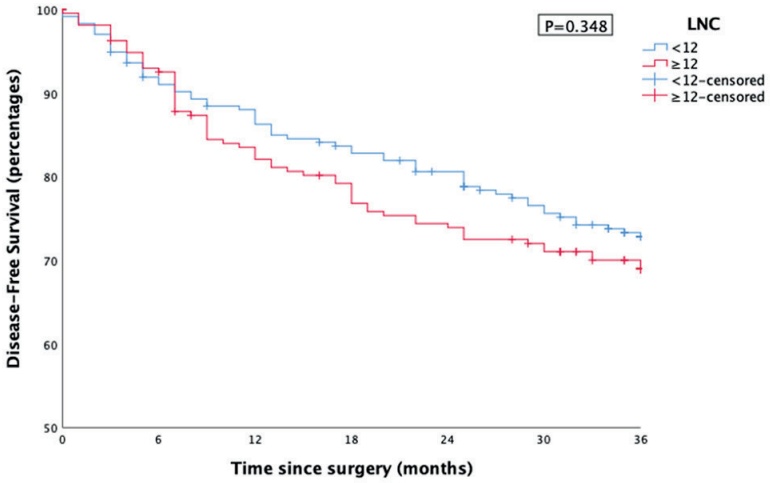
Figure 1 | Flowchart of included rectal cancer patients from the Snapshot study cohort for analysis. CRT, chemoradiotherapy.

Univariable survival analysis for LNC and LNR

In the whole study population, no statistically significant differences were found in the LNC (< 12 and ≥12) groups for 3-year DFS and OS (Figure 2). LNR was significantly associated with 3-year DFS and OS, with similar outcomes for any of the cut-off values (≤0.15, ≤0.20, and ≤0.30), as shown in Table 2. LNR was also significantly associated with 3-year DFS and OS in both the LNC < 12 and LNC ≥ 12 subgroups (Table 2).

In patients with positive nodal disease (ypN1-2), LNR was not significantly associated with 3-year DFS for any of the cut-off values (≤0.15, ≤0.20, and ≤0.30), although a clear trend was visualised (Figure 2A). No significant effect of LNR was seen regarding DFS in either of the ypN1 and ypN2 subgroups separately. LNR was significantly associated with 3-year OS for all cut-off values in patients with ypN1 -2 stage (Figure 2B). Within the node-positive subgroups, LNR was only significantly associated with OS in the ypN1 subgroup (91% vs. 77%, p = 0.040) using a cut-off value of 0.15 (Figure 3A), and in the ypN2 subgroup (100% vs. 58%, p = 0.030) using a cut-off of 0.30 (Figure 3B).

(A) Kaplan Meier of Disease-Free Survival in rectal cancer patients who underwent neoadjuvant chemoradiotherapy, stratified for LNC groups using cut-off of 12 lymph nodes.

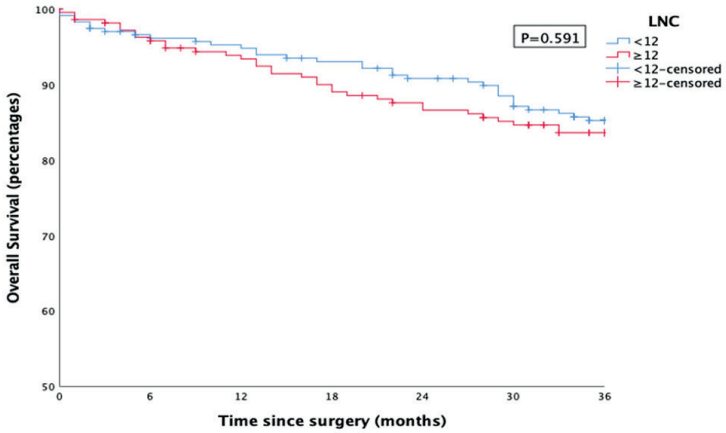


Patients at risk	0 months	6 months	12 months	18 months	24 months	30 months	36 months
LNC <12	236	214	204	192	182	168	153
LNC ≥12	216	199	176	166	156	149	137

Note: Y-axis has been formatted to end at 50%.

(B)

Kaplan Meier of Overall Survival in rectal cancer patients who underwent neoadjuvant chemoradiotherapy, stratified for LNC groups using cut-off of 12 lymph nodes.

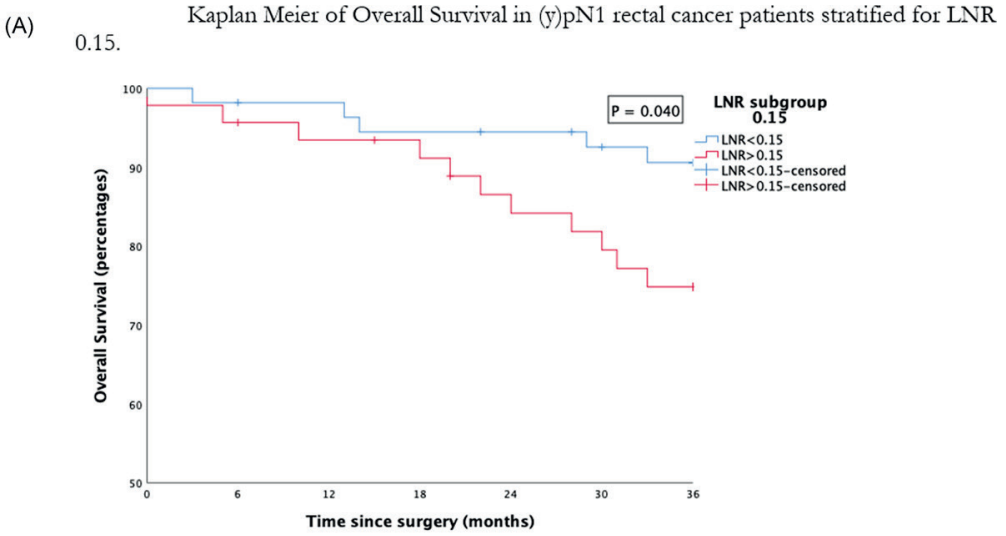


Patients at risk	0 months	6 months	12 months	18 months	24 months	30 months	36 months
LNC <12	235	221	216	209	201	193	177
LNC ≥12	216	205	195	187	179	173	160-

Note: Y-axis has been formatted to end at 50%.

Figure 2 | (A) Kaplan–Meier of disease-free survival in rectal cancer patients who underwent neoadjuvant chemoradiotherapy, stratified for LNC groups using cut-off of 12 lymph nodes. *(B) Kaplan–Meier of overall survival in rectal cancer patients who underwent neoadjuvant chemoradiotherapy, stratified for LNC groups using cut-off of 12 lymph nodes. LNC, lymph node count.*

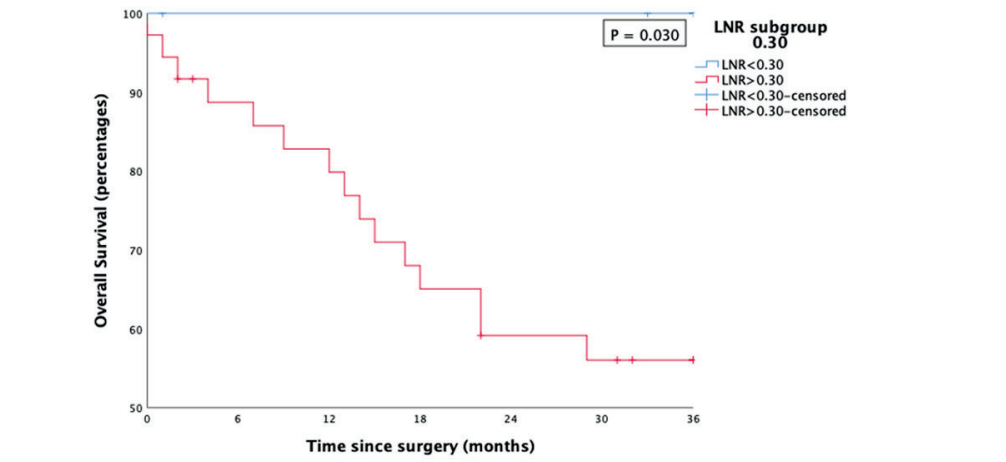
(A)



Patients at risk	0 months	6 months	12 months	18 months	24 months	30 months	36 months
LNR <0.15	55	54	53	51	50	49	47
LNR ≥0.15	46	45	43	42	38	35	33

Note: Y-axis has been formatted to start at 50%.

(B)



Patients at risk	0 months	6 months	12 months	18 months	24 months	30 months	36 months
LNR <0.30	9	8	8	8	8	8	7
LNR ≥0.30	36	31	28	24	20	19	17

Note: Y-axis has been formatted to start at 50%.

Figure 3 | (A) Kaplan–Meier of overall survival in (y)pN1 rectal cancer patients stratified for LNR 0.15. *(B) Kaplan–Meier of overall survival in (y)pN2 rectal cancer patients stratified for LNR 0.30. LNR, lymph node ratio.*

Multivariable survival analysis

Because LNC did not reveal any association with DFS or OS in univariable analysis, LNC was not tested in a multivariable model. For the whole study cohort, multivariable analyses of DFS and OS were performed using the different cut-off values of LNR (Table S1).

Table 1 | Pathological, and long-term oncologic outcomes of the study cohort.

Pathological and long-term oncologic outcomes	Overall (*n* = 458)
Histological type[a]	
Adenocarcinoma	420/446 (94.2%)
Mucinous	10/446 (2.2%)
Singlet ring cell	1/446 (0.2%)
Other	15/446 (3.4%)
Pathological tumour stage	
ypT0/X	85/458 (18.6%)
ypT1	30/458 (6.6%)
ypT2	104/458 (22.7%)
ypT3	207/458 (45.2%)
ypT4	31/458 (6.8%)
Unknown	1/458 (0.2%)
Pathological nodal stage	
ypN0	311/458 (67.9%)
ypN1	102/458 (22.3%)
ypN2	45/458 (9.8%)
CRM	
Positive ≤1 mm	47/458 (10.3%)
Negative	307/458 (67.0%)
Unknown	104/458 (22.7%)
LN (median, IQR)	11 [7–14]
LNC	
< 12	240/458 (52.4%)
≥12	218/458 (47.6%)
LNC < 12	
CRT-surgery interval<14 weeks	108/224 (48.2%)
CRT-surgery interval≥14 weeks	148/251 (59.0%)

Positive LNs (median, IQR)	2 [1–4]
Follow-up months (median, IQR)	43 [34–47]
3 years local recurrence (Kaplan–meier)	24/458 (5.2%)
3 years distant recurrence (Kaplan–meier)	86/458 (18.8%)
3 years disease-free survival (Kaplan–meier)	331/458 (72.3%)
3 years overall survival (Kaplan–meier)[b]	388/457 (84.9%)

Note: Values are given as n (%) or median (IQR).
Abbreviations: CRM, circumferential resection margin; LNC, lymph node count; LN, lymph node; LNR, lymph node ratio; IQR, Interquartile range.
[a]2 missing values.
[b]Missing value.

Besides LNR, factors that revealed an association with DFS in univariable analysis ($p < 0.10$) were ASA-score, distance to the ARJ, ypN stage, CRM, positive lymph nodes (continuous variable), multivisceral resection, and type of surgical procedure. When corrected for these factors in multivariable analysis, LNR was no longer significantly associated with DFS (cut-off ≤0.15: $p = 0.399$; cut-off ≤0.20: $p = 0.362$; cut-off ≤0.30: $p = 0.246$).
Factors associated with OS in univariable analysis ($p < 0.10$) were LNR, distance to the ARJ, ypN stage, CRM, positive lymph nodes, multivisceral resection, and type of surgical procedure (Table S2). In multivariable analysis, LNR was not significantly associated with OS for any of the cut-off values ($p = 0.529$, $p = 0.777$, and $p = 0.991$, respectively). For the ypN1-2 subgroup, additional uni-/ and multivariable analyses were performed of OS using the different cut-off values of LNR (Table S3). The following variables revealed significance for OS in univariable analysis: ypN, CRM, total amount of positive lymph nodes, surgical procedure, time-interval CRT-surgery, and LNR with cut-off value of 0.15 ($p = 0.026$) and 0.20 ($p = 0.015$). In multivariable analysis, LNR was no longer significantly associated with OS for any of the cut-off values ($p = 0.844$, $p = 0.787$, and $p = 0.895$, respectively).
Finally, for the ypN1 and ypN2 subgroups, the same uni-/and multivariable analyses of OS were performed. In the ypN1 subgroup, procedure and time-interval CRT-surgery were statistically significant for OS in the univariable analysis. None of the three LNR were significantly associated with OS in multivariable analysis (LNR: 0.15 ($p = 0.285$), LNR: 0.20 ($p = 0.186$), LNR: 0.30 ($p = 0.571$)). For ypN2, CRM + and total amount of positive lymph nodes revealed significance for OS in univariable analysis. However, the total amount of events was too small in the ypN2 subgroup to perform multivariable analysis.

Table 2 | Kaplan–Meier and univariable cox regression analysis of LNC using a cut-off value of 12 and LNR using different cut-off values with disease-free survival and overall survival as endpoints.

			Disease Free Survival		Overall Survival		Disease Free Survival	Overall Survival
Subgroups	LNR	No. of patients	3-year % (KM)	p-Value	3-year % (KM)	p-Value[1]	HR (95% CI)	HR (95% CI)
LNC<12		240	74.2%	0.348	85.9%	0.591	ref	ref
LNC≥12		218	70.2%		84.3%		1.18 (0.83-1.67)	1.31 (0.69-2.50)
	≤0.15	366	77.9%	**<0.001**	88.5%	**<0.001**	ref	ref
	>0.15	90	48.9%		71.1%		2.84 (1.98-4.08)*	4.48 (2.35-8.55)*
(y)pN1-2[3]	≤0.15	51	60.8%	0.076	90.2%	**0.007**	ref	ref
	>0.15	90	48.9%		71.1%		1.59 (0.94-2.69)	3.06 (1.04-9.04)*
(y)pN1	≤0.15	55	60.0%	0.282	90.9%	**0.040**	ref	ref
	>0.15	47	53.2%		76.6%		1.38 (0.76-2.49)	1.87 (0.59-5.91)
(y)pN2	≤0.15	3	66.7%	0.583	100%	0.324	ref	ref
	>0.15	42	42.9%		64.3%		1.73 (0.23-12.82)	NA[2]
LNC<12	≤0.15	182	81.3%	**<0.001**	90.1%	**<0.001**	ref	ref
	>0.15	56	50.0%		71.4%		3.35 (2.03-5.54)*	5.52 (2.10-14.50)*
LNC≥12	≤0.15	184	74.5%	**<0.001**	86.9%	**0.013**	ref	ref
	>0.15	34	47.1%		70.6%		2.50 (1.47-4.36)*	4.11 (1.68-10.07)*
	≤0.20	377	76.9%	**<0.001**	88.0%	**<0.001**	ref	ref
	>0.20	79	49.4%		70.9%		2.66 (1.83-3.87)*	4.83 (2.53-9.22)*
(y)pN1-2[3]	≤0.20	62	58.1%	0.161	87.1%	**0.013**	ref	ref
	>0.20	79	49.4%		70.9%		1.41 (0.86-2.30)	3.23 (1.19-8.77)*
(y)pN1	≤0.20	64	57.8%	0.556	87.5%	0.206	ref	ref
	>0.20	38	55.3%		78.9%		1.20 (0.65-2.20)	1.90 (0.61-5.88)
(y)pN2	≤0.20	4	50.0%	0.953	100%	0.224	ref	ref
	>0.20	41	43.9%		63.4%		0.96 (0.23-4.07)	NA[2]
LNC<12	≤0.20	189	80.4%	**<0.001**	89.4%	**<0.001**	ref	ref
	>0.20	49	49.0%		71.4%		3.25 (1.95-5.41)*	6.67 (2.54-17.54)*
LNC≥12	≤0.20	188	73.4%	**0.005**	86.6%	**0.013**	ref	ref
	>0.20	30	50.0%		70.0%		2.23 (1.25-3.97)*	3.98 (1.59-9.99)*
	≤0.30	396	75.8%	**<0.001**	87.3%	**<0.001**	ref	ref
	>0.30	60	48.3%		70.0%		2.56 (1.71-3.84)*	4.27 (2.17-8.39)*
(y)pN1-2[3]	≤0.30	81	56.8%	0.210	84.0%	**0.032**	ref	ref
	>0.30	60	48.3%		70.0%		1.35 (0.83-2.18)	2.30 (0.98-5.38)
(y)pN1	≤0.30	78	56.4%	0.978	83.3%	0.605	ref	ref
	>0.30	24	58.3%		87.5%		0.99 (0.49-2.01)	0.62 (0.14-2.84)
(y)pN2	≤0.30	9	55.6%	0.560	100%	**0.030**	ref	ref
	>0.30	36	41.7%		58.3%		1.37 (0.50-3.99)	NA[2]
LNC<12	≤0.30	198	78.8%	**<0.001**	87.9%	**0.020**	ref	ref
	>0.30	40	50.0%		75.0%		2.78 (1.63-4.74)*	3.95 (1.50-10.38)*
LNC≥12	≤0.30	198	72.7%	**0.002**	86.8%	**<0.001**	ref	ref
	>0.30	20	45.0%		60.0%		2.61 (1.37-5.00)*	5.71 (2.19-14.88)*

Note: Bold values P < 0.05.

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio based on univariable cox regression analysis; KM, Kaplan–Meier; LNR, lymph node ratio; NA, not analysed, too small numbers to run cox regression analysis; OS, overall survival; LNC, lymph node count; ref, reference.

[a]Tested by log-rank test.

[b]Number of events too small for cox-regression analyses.

[c]6/317 patients were incorrectly registered as having negative lymph nodes, but having ypN1-2 disease.

**p < 0.05.*

DISCUSSION

This multicentre cross-sectional study showed that LNC with a cut-off of 12 lymph nodes did not reveal a prognostic impact in surgically treated locally advanced rectal cancer patients after neoadjuvant CRT. In univariable analysis, LNR was significantly associated with both DFS and OS ($p < 0.001$). This association disappeared in multivariable analysis after correction for N-stage, indicating that LNR is not a significant prognostic factor when N-stage is considered. Within the subgroup of patients with positive nodal disease, LNR showed a significant association with OS but not with DFS. However, significance of these associations was lost when corrected for confounders such as CRM involvement and total amount of positive lymph nodes. Although based on small numbers, LNR was able to identify patients with excellent survival among those with ypN2 disease, reaching statistical significance for cut-off 0.30 in univariable analysis.

This indicates that LNC and LNR are not of additional value besides N-stage in rectal cancer patients who underwent neoadjuvant CRT, but that LNR might have a role in identifying patients with a different prognosis among specific node-positive subgroups.

In accordance with our findings, Awwad et al.[23] reported no statistically significant effect of LNC on OS in rectal cancer patients after CRT in their systematic review. LNC after CRT not meeting the minimum requirement of 12 lymph nodes is often reported, however, it is unclear whether this is of clinical or prognostic importance.[9,24,25]

Remarkably, the survival curves of patients with LNC < 12 were even above those with higher LNC (Figure 2). The number of benign lymph nodes will be sparser in surgical specimens through lymphoid tissue involution after neo-adjuvant treatment.[26,27] Malignant lymph nodes will decrease as an expression of tumour regression and could be considered of prognostic benefit.[28,29] A longer interval from neoadjuvant therapy to surgery has also been shown to decrease lymph node yield, which was reproduced in our data.[8] Finally, differences between and within laboratories will explain some of the variance in lymph node yield.[9] Therefore, the number of lymph nodes after CRT does not reflect surgical quality.

Alternative prognosticators to LNC such as LNR have been extensively investigated. Significant associations between LNR and OS have been reported, although cut-off values differ greatly between studies.[18–22,30,31] The results of the present study also showed a significant association of LNR with both DFS and OS in univariable analysis for any of the tested cut-off values.

The strongest effects based on HRs were found for the lowest cut-off value (0.15), but the absolute survival probabilities were very similar for each of the cut-off values. A recently published study by Fulop et al.32 with a 0.15 cut-off level also found a significant association between LNR and OS in 186 patients with Stage II–III rectal cancer who underwent neoadjuvant CRT. Furthermore, this study showed that LNR was inversely related to 3-years DFS and OS. In the study of Lee et al.,22 this effect of increasing LNR and decreasing DFS (LNR ≤ 0.15; 66.7%, ≤0.20; 64.1%, and ≤0.30; 63.7%) and OS (LNR ≤ 0.15; 90.3%, ≤0.20; 87.2%, and ≤0.30; 85.7%) was also demonstrated, although absolute differences were small.[22] This indicates that the actual cut-off value used might result in only small differences in outcome.

LNR is considered more than a reflection of nodal status, because it brings the promise of preventing understaging. Park et al.[33] showed that a LNR ≤ 0.25 and nodal stage are prognostic factors for OS in 967 patients with locally advanced rectal cancer treated without neo-

adjuvant treatment.[33] In case of CRT, significantly less lymph nodes were harvested ($p < 0.001$) and the predictive value of pN stage was lost, but LNR remained a prognostic factor in multivariable analysis. This is in contrast to the present study, in which LNR lost its significance when corrected for N-stage.

Although numbers were small with large confidence intervals, we found a high (100% 3 year) OS in the ypN2 low LNR group for all cut-off points compared with poorer prognosis for the ypN2 high LNR group for cut-off 0.15 (64.3%), 0.20 (63.4%), and 0.30 (58.5%). Due to a small number of events, this was only statistically significant in the LNR 0.30 group ($p = 0.032$). Koo et al.[20] retrospectively analysed 638 patients who had undergone TME surgery for rectal carcinoma after CRT, with an LNR cut-off at 0.15. They showed that the high LNR ypN1 group had a poorer OS ($p = 0.043$) and DFS ($p = 0.056$) than the low LNR pN1 group. They found no difference between the high LNR ypN1 group and the whole ypN2 group in terms of OS ($p = 0.703$) and DFS ($p = 0.831$). Kang and Lee have also shown that LNR could help to differentiate subgroups of prognostic significance in rectal cancer patients receiving TME surgery after CRT within the pN+ subgroup.[22,34] The recent ADORE trial compared adjuvant FOLFOX to FL in rectal cancer patients who received CRT and TME surgery. The study shows an increased DFS in the FOLFOX group, specifically in the ypN1b (HR 0.36, $p = 0.04$) and ypN2 (HR 0.41, $p = 0.04$) subgroups.[35]

Based on these results, LNR can identify high-risk node positive patients and possibly guide the use of (intensified) adjuvant therapy after neoadjuvant therapy better then ypN stage, thereby sparing unnecessary treatment with associated morbidity for a subset of patients and maximising results for others. LNR-based identification of certain prognostically different subgroups can be further explored by looking into molecular profiles and specific mutations. Further research might look at LNR as potential biomarker among node-positive patients, besides other histological (e.g., extramural vascular invasion) as well as molecular markers.

The strength of this cross-sectional study is the relatively large group of patients with almost similar follow-up duration due to the cross-sectional study design. Limitations of this study are related to the selection of Dutch hospitals based on voluntary participation, which might have resulted in hospitals with a specific level of performance in rectal cancer care, not representing the whole country. Inherent to the retrospective design, there were missing data of included variables and this could have resulted in information bias. Also, the number of events in our subset analysis were small showing a need for confirmation of our findings in other series. Finally, adjuvant chemotherapy after TME surgery is not the standard of care in the Netherlands. Therefore, these results can not readily be compared with series from countries where it is common practice.

This multicentre cross-sectional study showed that less than 12 retrieved lymph nodes in a TME specimen after CRT is not correlated with worse DFS and OS. Similarly, LNR did not add any prognostic information besides pN stage for the whole group of patients treated with neoadjuvant CRT. However, this study suggests that LNR might enable identification of patients within the node-positive subgroups with a favourable outcome.

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SUPPLEMENTARY MATERIALS

Supplement Table 1a | Uni-and multivariable analysis of Disease-Free Survival in the whole group of rectal cancer patients treated with neoadjuvant CRT, analysing LNR 0.15 as a prognostic factor.

Variable		Univariable analysis		Multivariable analysis	
		HR (95% CI)	P-value	aHR (95% CI)	P-value
Gender	Male	1.18 (0.82-1.70)	0.378		
	Female	Ref			
Age	<75	Ref			
	≥75	1.21 (0.75-1.98)	0.439		
BMI	<30	Ref			
	≥30	0.97 (0.57-1.63)	0.894		
ASA-score	I/II	Ref			
	III/IV	**1.81 (1.13-2.89)**	**0.013**	**1.99 (1.05-3.78)**	**0.035**
Distance to the ARJ	<3cm	**1.80 (1.04-3.10)**	**0.036**	1.77 (0.83-3.74)	0.138
	3.1-7cm	**1.69 (0.97-2.97)**	**0.066**	1.51 (0.79-2.88)	0.215
	>7cm	Ref			
Tumour stage	ypT1-3	Ref			
	ypT4	1.44 (0.81-2.55)	0.220		
Nodal stage	ypN0	Ref			
	ypN1	**2.56 (1.73-3.80)**	**<0.001**	**2.31 (1.22-4.36)**	**0.010**
	ypN2	**3.83 (2.40-6.13)**	**<0.001**	1.68 (0.46-6.11)	0.432
CRM	Positive	**3.21 (2.08-4.95)**	**<0.001**	**2.54 (1.47-4.39)**	**0.001**
	Negative	Ref			
Lymph nodes retrieved		1.01 (0.98-1.04)	0.466		
Positive lymph nodes		**1.19 (1.14-1.25)**	**<0.001**	**1.14 (1.02-1.28)**	**0.027**
LNR	≤0.15	Ref			
	>0.15	**2.84 (1.98-4.08)**	**<0.001**	1.40 (0.64-3.05)	0.399
Multivisceral resection	Yes	**2.28 (1.50-3.48)**	**<0.001**	**2.18 (1.24-3.85)**	**0.007**
Approach	Open	Ref			
	Laparoscopic	1.03 (0.73-1.47)	0.851		
	Laparoscopic conversion	2.18 (0.69-6.95)	0.187		
Procedure	LAR	Ref			
	APR	**1.48 (1.01-2.16)**	**0.043**	1.05 (0.58-1.92)	0.863
	Hartmann	0.99 (0.57-1.73)	0.976	-	-
Interval CRT-surgery (weeks)	<14 weeks	Ref			
	≥14 weeks	1.19 (0.84-1.68)	0.340		

Variables with P-values <0.10 in univariable analyses were used in the multivariable model. P-values <0.05 were considered statistically significant.

BMI Body Mass Index, ASA American Society of Anaesthesiologists-Classification, CRM Circumferential Resection Margin, LAR Low Anterior Resection, APR AbdominoPerineal Resection, LNR Lymph node Ratio.

Supplement Table 1b | Uni-and multivariable analysis of Disease-Free Survival in the whole group of rectal cancer patients treated with neoadjuvant CRT, analysing LNR 0.20 as a prognostic factor.

Variable		Univariable analysis		Multivariable analysis	
		HR (95% CI)	P-value	aHR (95% CI)	P-value
Gender	Male	1.18 (0.82-1.70)	0.378		
	Female	Ref			
Age	<75	Ref			
	≥75	1.21 (0.75-1.98)	0.439		
BMI	<30	Ref			
	≥30	0.97 (0.57-1.63)	0.894		
ASA-score	I/II	Ref			
	III/IV	**1.81 (1.13-2.89)**	**0.013**	**2.01 (1.06-3.81)**	**0.033**
Distance to the ARJ	<3cm	**1.80 (1.04-3.10)**	**0.036**	1.76 (0.83-3.74)	0.138
	3.1-7cm	**1.69 (0.97-2.97)**	**0.066**	1.49 (0.78-2.84)	0.233
	>7cm	Ref			
Tumour stage	ypT1-3	Ref			
	ypT4	1.44 (0.81-2.55)	0.220		
Nodal stage	ypN0	Ref			
	ypN1	**2.56 (1.73-3.80)**	**<0.001**	**2.31 (1.24-4.30)**	**0.008**
	ypN2	**3.83 (2.40-6.13)**	**<0.001**	1.75 (0.47-6.47)	0.404
CRM	Positive	**3.21 (2.08-4.95)**	**<0.001**	**2.54 (1.47-4.39)**	**0.001**
	Negative	Ref			
Lymph nodes retrieved		1.01 (0.98-1.04)	0.466		
Positive lymph nodes		**1.19 (1.14-1.25)**	**<0.001**	**1.14 (1.02-1.28)**	**0.025**
LNR	≤0.20	Ref			
	>0.20	**2.66 (1.83-3.87)**	**<0.001**	1.47 (0.64-3.35)	0.362
Multivisceral resection	Yes	**2.28 (1.50-3.48)**	**<0.001**	**2.21 (1.25-3.90)**	**0.006**
Approach	Open	Ref			
	Laparoscopic	1.03 (0.73-1.47)	0.851		
	Laparoscopic conversion	2.18 (0.69-6.95)	0.187		
Procedure	LAR	Ref			
	APR	**1.48 (1.01-2.16)**	**0.043**	1.05 (0.57-1.90)	0.886
	Hartmann	0.99 (0.57-1.73)	0.976	-	-
Interval CRT-surgery (weeks)	<14 weeks	Ref			
	≥14 weeks	1.19 (0.84-1.68)	0.340		

Abbrevations: BMI = Body Mass Index, ASA = American Society of Anaesthesiologists-Classification, CRM = Circumferential Resection Margin, LAR = Low Anterior Resection, APR = AbdominoPerineal Resection, LNR = Lymph node Ratio.

**Variables with P-values <0.10 in univariable analyses were used in the multivariable model. P-values <0.05 were considered statistically significant.*

Supplement Table 1c | Uni-and multivariable analysis of Disease-free Survival in the whole group of rectal cancer patients treated with neoadjuvant CRT, analysing LNR 0.30 as a prognostic factor.

Variable		Univariable analysis		Multivariable analysis	
		HR (95% CI)	P-value	aHR (95% CI)	P-value
Gender	Male	1.18 (0.82-1.70)	0.378		
	Female	Ref			
Age	<75	Ref			
	≥75	1.21 (0.75-1.98)	0.439		
BMI	<30	Ref			
	≥30	0.97 (0.57-1.63)	0.894		
ASA-score	I/II	Ref			
	III/IV	**1.81 (1.13-2.89)**	**0.013**	**2.11 (1.11-4.03)**	**0.023**
Distance to the ARJ	<3cm	**1.80 (1.04-3.10)**	**0.036**	1.68 (0.80-3.53)	0.174
	3.1-7cm	**1.69 (0.97-2.97)**	**0.066**	1.42 (0.74-2.73)	0.292
	>7cm	Ref			
Tumour stage	ypT1-3	Ref			
	ypT4	1.44 (0.81-2.55)	0.220		
Nodal stage	ypN0	Ref			
	ypN1	**2.56 (1.73-3.80)**	**<0.001**	**2.17 (1.24-3.80)**	**0.007**
	ypN2	**3.83 (2.40-6.13)**	**<0.001**	1.67 (0.52-5.39)	0.393
CRM	Positive	**3.21 (2.08-4.95)**	**<0.001**	**2.54 (1.47-4.38)**	**0.001**
	Negative	Ref			
Lymph nodes retrieved		1.01 (0.98-1.04)	0.466		
Positive lymph nodes		**1.19 (1.14-1.25)**	**<0.001**	**1.15 (1.03-1.30)**	**0.017**
LNR	≤0.30	Ref			
	>0.30	**2.56 (1.71-3.84)**	**<0.001**	1.63 (0.71-3.74)	0.246
Multivisceral resection	Yes	**2.28 (1.50-3.48)**	**<0.001**	**2.17 (1.23-3.82)**	**0.007**
Approach	Open	Ref			
	Laparoscopic	1.03 (0.73-1.47)	0.851		
	Laparoscopic conversion	2.18 (0.69-6.95)	0.187		
Procedure	LAR	Ref			
	APR	**1.48 (1.01-2.16)**	**0.043**	1.08 (0.56-2.09)	0.823
	Hartmann	0.99 (0.57-1.73)	0.976	-	-
Interval CRT-surgery (weeks)	<14 weeks	Ref			
	≥14 weeks	1.19 (0.84-1.68)	0.340		

Abbrevations: BMI = Body Mass Index, ASA = American Society of Anaesthesiologists-Classification, CRM = Circumferential Resection Margin, LAR = Low Anterior Resection, APR = AbdominoPerineal Resection, LNR = Lymph node Ratio.

**Variables with P-values <0.10 in univariable analyses were used in the multivariable model. P-values <0.05 were considered statistically significant.*

Supplement Table 2a | Uni-and multivariable analysis of Overall Survival in the whole group of rectal cancer patients treated with neoadjuvant CRT, analysing LNR 0.15 as a prognostic factor.

Variable		Univariable analysis		Multivariable analysis	
		HR (95% CI)	P-value	aHR (95% CI)	P-value
Gender	Male	0.88 (0.46-1.70)	0.712		
	Female	Ref			
Age	<75	Ref			
	≥75	0.88 (0.31-2.48)	0.804		
BMI	<30	Ref			
	≥30	1.00 (0.39-2.58)	0.996		
ASA-score	I/II	Ref			
	III/IV	0.82 (0.25-2.69)	0.749		
Distance to the ARJ	<3cm	**2.60 (0.94-7.14)**	**0.065**	2.22 (0.78-6.31)	0.136
	3.1-7cm	1.69 (0.57-5.05)	0.346	-	-
	>7cm	Ref			
Tumour stage	ypT1-3	Ref			
	ypT4	1.40 (0.49-3.95)	0.530		
Nodal stage	ypN0	Ref			
	ypN1	**2.57 (1.19-5.56)**	**0.016**	2.39 (0.71-8.02)	0.160
	ypN2	**7.07 (3.21-15.59)**	**<0.001**	4.19 (0.50-34.96)	0.186
CRM	Positive	**5.45 (2.70-11.02)**	**<0.001**	**3.79 (1.60-8.94)**	**0.002**
	Negative	Ref			
Lymph nodes retrieved		1.02 (0.97-1.07)	0.493		
Positive lymph nodes		**1.28 (1.19-1.37)**	**<0.001**	1.15 (0.98-1.35)	0.097
LNR	≤0.15	Ref			
	>0.15	**4.48 (2.35-8.55)**	**<0.001**	0.62 (0.14-2.76)	0.529
Multivisceral resection	Yes	**2.54 (1.20-5.41)**	**0.015**	**2.77 (1.11-6.89)**	**0.028**
Approach	Open	Ref			
	Laparoscopic	1.12 (0.58-2.15)	0.733		
	Laparoscopic conversion	2.60 (0.35-19.47)	0.353		
Procedure	LAR	Ref			
	APR	**2.32 (1.09-4.93)**	**0.029**	0.80 (0.28-2.32)	0.682
	Hartmann	1.65 (0.60-4.55)	0.330	-	-
Interval CRT-surgery (weeks)	<14 weeks	Ref			
	≥14 weeks	0.59 (0.31-1.15)	0.123		

Abbrevations: BMI = Body Mass Index, ASA = American Society of Anaesthesiologists-Classification, CRM = Circumferential Resection Margin, LAR = Low Anterior Resection, APR = AbdominoPerineal Resection, LNR = Lymph node Ratio.

**Variables with P-values <0.10 in univariable analyses were used in the multivariable model. P-values <0.05 were considered statistically significant.*

Supplement Table 2b | Uni-and multivariable analysis of Overall Survival in the whole group of rectal cancer patients treated with neoadjuvant CRT, analysing LNR 0.20 as a prognostic factor.

Variable		Univariable analysis		Multivariable analysis	
		HR (95% CI)	P-value	aHR (95% CI)	P-value
Gender	Male	0.88 (0.46-1.70)	0.712		
	Female	Ref			
Age	<75	Ref			
	≥75	0.88 (0.31-2.48)	0.804		
BMI	<30	Ref			
	≥30	1.00 (0.39-2.58)	0.996		
ASA-score	I/II	Ref			
	III/IV	0.82 (0.25-2.69)	0.749		
Distance to the ARJ	<3cm	**2.60 (0.94-7.14)**	**0.065**	2.19 (0.76-6.30)	0.148
	3.1-7cm	1.69 (0.57-5.05)	0.346	-	-
	>7cm	Ref			
Tumour stage	ypT1-3	Ref			
	ypT4	1.40 (0.49-3.95)	0.530		
Nodal stage	ypN0	Ref			
	ypN1	**2.57 (1.19-5.56)**	**0.016**	2.12 (0.62-7.23)	0.232
	ypN2	**7.07 (3.21-15.59)**	**<0.001**	3.31 (0.39-27.97)	0.271
CRM	Positive	**5.45 (2.70-11.02)**	**<0.001**	**3.79 (1.60-8.97)**	**0.002**
	Negative	Ref			
Lymph nodes retrieved		1.02 (0.97-1.07)	0.493		
Positive lymph nodes		**1.28 (1.19-1.37)**	**<0.001**	1.14 (0.97-1.34)	0.105
LNR	≤0.20	Ref			
	>0.20	**4.83 (2.53-9.22)**	**<0.001**	0.80 (0.17-3.70)	0.777
Multivisceral resection	Yes	**2.54 (1.20-5.41)**	**0.015**	**2.76 (1.11-6.88)**	**0.030**
Approach	Open	Ref			
	Laparoscopic	1.12 (0.58-2.15)	0.733		
	Laparoscopic conversion	2.60 (0.35-19.47)	0.353		
Procedure	LAR	Ref			
	APR	**2.32 (1.09-4.93)**	**0.029**	0.80 (0.27-2.33)	0.677
	Hartmann	1.65 (0.60-4.55)	0.330	-	-
Interval CRT-surgery (weeks)	<14 weeks	Ref			
	≥14 weeks	0.59 (0.31-1.15)	0.123		

Abbrevations: BMI = Body Mass Index, ASA = American Society of Anaesthesiologists-Classification, CRM = Circumferential Resection Margin, LAR = Low Anterior Resection, APR = AbdominoPerineal Resection, LNR = Lymph node Ratio.

**Variables with P-values <0.10 in univariable analyses were used in the multivariable model. P-values <0.05 were considered statistically significant.*

Supplement Table 2c | Uni-and multivariable analysis of Overall Survival in the whole group of rectal cancer patients treated with neoadjuvant CRT, analysing LNR 0.30 as a prognostic factor.

Variable		Univariable analysis		Multivariable analysis	
		HR (95% CI)	P-value	aHR (95% CI)	P-value
Gender	Male	0.88 (0.46-1.70)	0.712		
	Female	Ref			
Age	<75	Ref			
	≥75	0.88 (0.31-2.48)	0.804		
BMI	<30	Ref			
	≥30	1.00 (0.39-2.58)	0.996		
ASA-score	I/II	Ref			
	III/IV	0.82 (0.25-2.69)	0.749		
Distance to the ARJ	<3cm	**2.60 (0.94-7.14)**	**0.065**	2.15 (0.74-6.20)	0.160
	3.1-7cm	1.69 (0.57-5.05)	0.346	-	-
	>7cm	Ref			
Tumour stage	ypT1-3	Ref			
	ypT4	1.40 (0.49-3.95)	0.530		
Nodal stage	ypN0	Ref			
	ypN1	**2.57 (1.19-5.56)**	**0.016**	1.92 (0.65-5.73)	0.241
	ypN2	**7.07 (3.21-15.59)**	**<0.001**	2.72 (0.44-16.65)	0.279
CRM	Positive	**5.45 (2.70-11.02)**	**<0.001**	**3.77 (1.59-8.96)**	**0.003**
	Negative	Ref			
Lymph nodes retrieved		1.02 (0.97-1.07)	0.493		
Positive lymph nodes		**4.27 (2.17-8.39)**	**<0.001**	1.14 (0.97-1.35)	0.123
LNR	≤0.30	Ref			
	>0.30	**4.83 (2.53-9.22)**	**<0.001**	0.99 (0.26-3.78)	0.991
Multivisceral resection	Yes	**2.54 (1.20-5.41)**	**0.015**	**2.73 (1.10-6.79)**	**0.031**
Approach	Open	Ref			
	Laparoscopic	1.12 (0.58-2.15)	0.733		
	Laparoscopic conversion	2.60 (0.35-19.47)	0.353		
Procedure	LAR	Ref			
	APR	**2.32 (1.09-4.93)**	**0.029**	0.80 (0.27-2.35)	0.687
	Hartmann	1.65 (0.60-4.55)	0.330	-	-
Interval CRT-surgery (weeks)	<14 weeks	Ref			
	≥14 weeks	0.59 (0.31-1.15)	0.123		

Abbrevations: BMI = Body Mass Index, ASA = American Society of Anaesthesiologists-Classification, CRM = Circumferential Resection Margin, LAR = Low Anterior Resection, APR = AbdominoPerineal Resection, LNR = Lymph node Ratio.

**Variables with P-values <0.10 in univariable analyses were used in the multivariable model. P-values <0.05 were considered statistically significant.*

Supplement Table 3 | Multivariable cox regression analysis of Overall Survival in the group of ypN1-2, ypN1 and ypN2 rectal cancer patients treated with neoadjuvant CRT, analysing LNR using different cut-off values as prognostic factors.

		Overall Survival	
		Multivariable analysis*	
		aHR	
Subgroups	LNR	(95% CI)	p-Value
ypN1-2[1]	≤0.15	ref	
	>0.15	1.15 (0.30-3.35)	0.844
ypN1	≤0.15	ref	
	>0.15	1.88 (0.59-5.95)	0.285
ypN2	≤0.15	ref	
	>0.15	NA[2]	NA
ypN1-2[1]	≤0.20	ref	
	>0.20	1.19 (0.33-4.33)	0.787
ypN1	≤0.20	ref	
	>0.20	2.17 (0.69-6.81)	0.186
ypN2	≤0.20	ref	
	>0.20	NA[2]	NA
ypN1-2[1]	≤0.30	ref	
	>0.30	0.93 (0.30-2.91)	0.895
ypN1	≤0.30	ref	
	>0.30	0.64 (0.14-2.95)	0.571
ypN2	≤0.30	ref	
	>0.30	NA[2]	NA

Abbrevations: LNR = Lymph node Ratio, aHR= hazard ratio based on univariable cox regression analysis, CI= confidence interval, ref = reference, NA= not analysed, too small numbers to run cox regression analysi

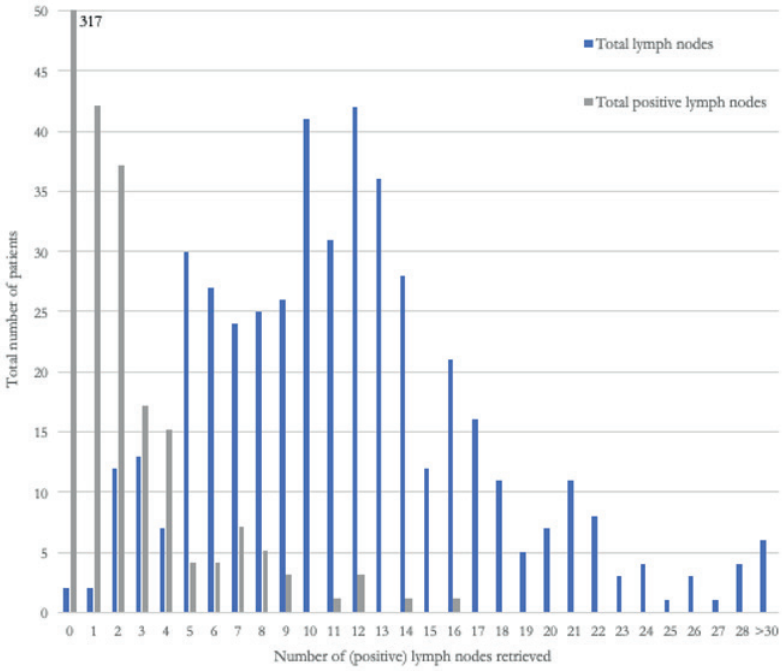
**Variables with P-values <0.10 in univariable analyses were used in the multivariable model. Variables tested in the multivariable model are not displayed here. P-values <0.05 were considered statistically significant.*

Notes:

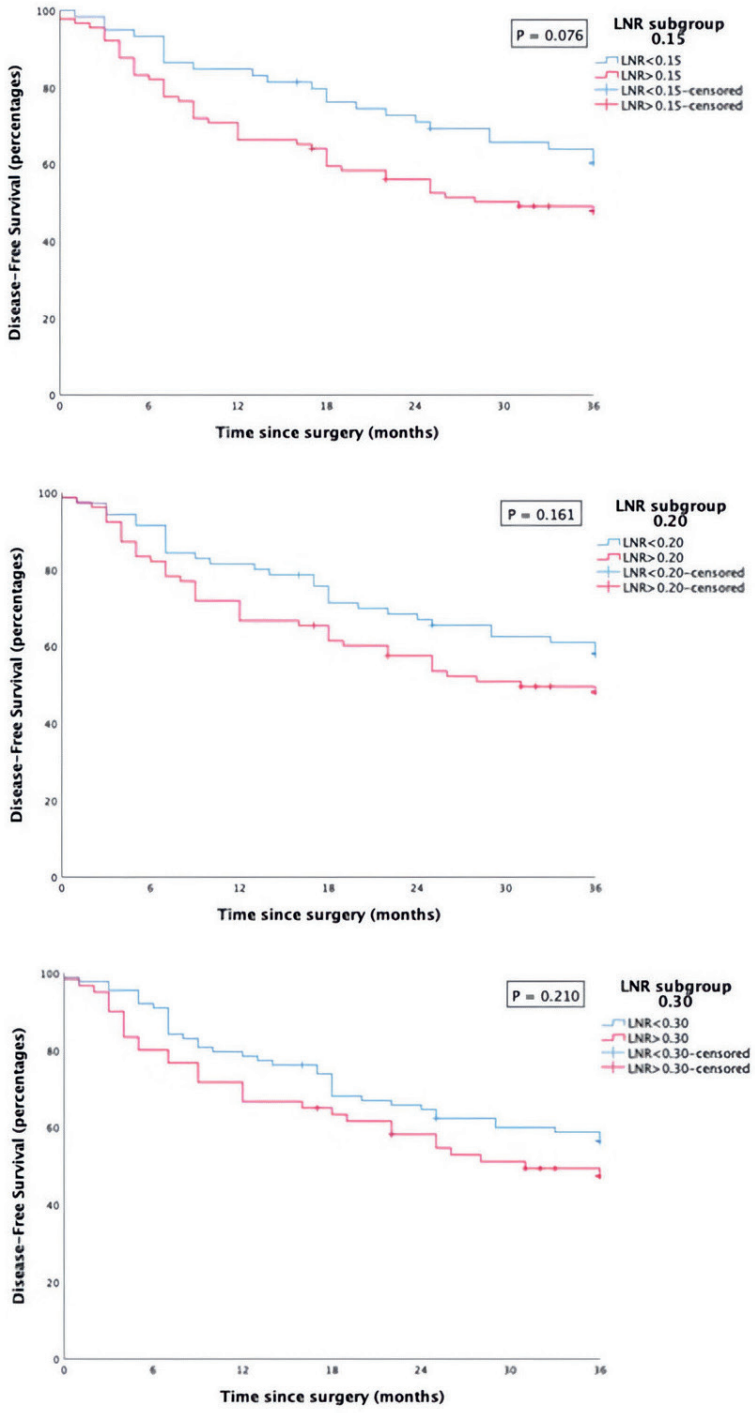
[1] 6/317 patients were incorrectly registered as having negative lymph nodes, but having ypN1-2 disease.

[x] Number of events too small for multivariable cox-regression analyses.

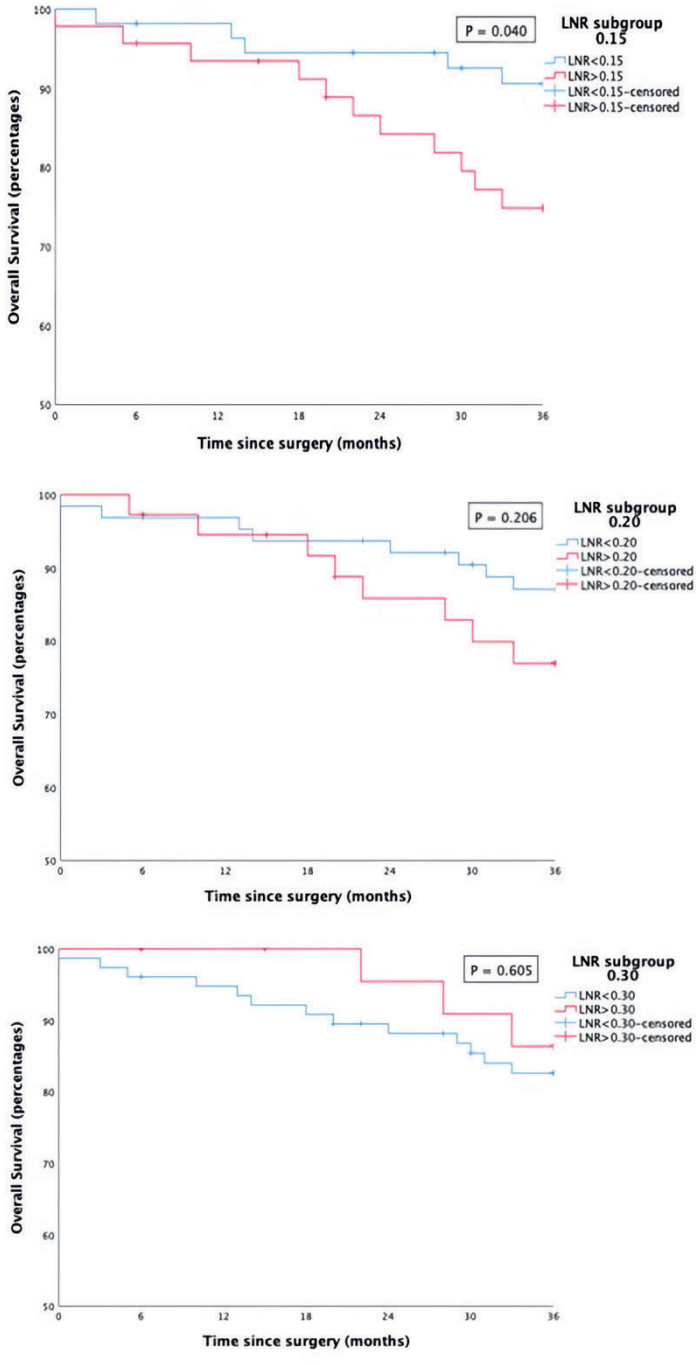
Supplement Figure 1| Amount of rectal cancer patients treated with CRT according to the total number of lymph nodes and total number of positive lymph notes retrieved.



* *Note 6/317 patients were incorrectly registered as having negative lymph nodes , but having pN1-2 disease*



Supplement Figure 2a | Kaplan Meier of overall survival in ypN1-2 patients stratified per LNR



Supplement Figure 2a | Kaplan-Meier of disease free survival in ypN1 patients stratified per LNR.

PART II

Patient perspective

CHAPTER 5

Delayed Surgery after Neoadjuvant Treatment for Rectal Cancer Does Not Lead to Impaired Quality of Life, Worry for Cancer, or Regret

Vincent Maurice Meyer, Richtje R Meuzelaar, Yvonne Schoenaker, Jan-Willem de Groot, Edwin de Boer, Onno Reerink, Wouter de Vos tot Nederveen Cappel, Geerard L Beets, Henderik L van Westreenen

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SIMPLE SUMMARY

Rectal cancer patients with an initial (near) complete clinical response to neoadjuvant chemoradiotherapy can be repeatedly assessed to see if a complete response endures. Up to 75% of these patients are able to avoid surgery and its related complications. However, the remaining 25% who 'fail' will eventually have to undergo surgery. Although recent studies have shown that patients undergoing delayed surgery have promising surgical and oncological outcomes, it is not known how these patients fare in terms of quality of life. The aim of this study was to compare quality of life between these immediate and delayed surgery groups through validated questionnaires. Our study including 51 patients shows no difference in quality of life, worry for cancer, or decision regret. Therefore, from a quality of life perspective, this study supports a repeated response assessment strategy after chemoradiotherapy for rectal carcinoma to identify all complete responders.

ABSTRACT

Non operative management of complete clinical responders after neoadjuvant treatment for rectal cancer enjoys an increasing popularity because of the increased functional outcome results. Even a near complete response can evolve in a cCR, and therefore further delaying response assessment is accepted. However, up to 40% of patients will develop a regrowth and will eventually require delayed surgery. It is presently unknown if and to what extent quality of life of these patients is affected, compared to patients who undergo immediate surgery. Between January 2015-May 2020, 200 patients were treated with neoadjuvant therapy of whom 94 received TME surgery. Fifty-one (59%) of 87 alive patients returned the questionnaires: 33 patients who underwent immediate and 18 patients who underwent delayed surgery. Quality of life was measured through the QLQ-C30, QLQ-CR29, and Cancer Worry Scale questionnaires. Regret to participate in repeated response assessment protocol was assessed through the Decision Regret Scale. Exploratory factor analysis (EFA) and a 'known groups comparison' was performed to assess QLQ questionnaires validity in this sample. Higher mean physical function scores (89.2 vs. 77.6, $p = 0.03$) were observed in the immediate surgery group, which lost significance after correction for operation type ($p = 0.25$). Arousal for men was higher in the delayed surgery group (20.0 vs. 57.1, $p = 0.02$). There were no differences between surgical groups for the other questionnaire items. Worry for cancer was lower in the delayed surgery group (10.8 vs. 14.0, $p = 0.21$). Regret was very low (12–16%). EFA reproduced most QLQ C-30 and CR29 subscales with good internal consistency. Quality of life is not impaired in patients undergoing delayed TME surgery after neoadjuvant treatment for rectal cancer. Moreover, there is very low regret and no increase in worry for cancer. Therefore, from a quality of life perspective, this study supports a repeated response assessment strategy after CRTx for rectal carcinoma to identify all complete responders.

Keywords

rectal cancer; watch and wait; neo-adjuvant treatment; non operative management

INTRODUCTION

Neoadjuvant chemoradiotherapy (CRTx) followed by total mesorectal excision (TME) surgery is the gold standard for locally advanced rectal carcinoma. A prognostic favorable subgroup of patients will develop a complete clinical response after CRTx. Increasing evidence shows that non-operative management (NOM) by a watch-and-wait (W&W) strategy leads up to 75% of patients avoiding surgery and its related complications, with excellent oncological results.[1,2] Therefore, W&W is gaining acceptance as an alternative to TME surgery.

However, it remains difficult to clinically identify a complete pathological response (pCR). Treatment related fibrosis and inflammation after CRTx impair the interpretation of digital rectal examination, MRI, endoscopy, and biopsies.[3–6] Response assessment is further complicated by the timing of examination. In a cohort of 49 patients with a near complete clinical response (near cCR) at 8–10 weeks, 90% (44) turned out to have a cCR at response assessment 6–12 weeks later.[7] True complete responders could even take 19 to 26 weeks to develop a cCR.[8] Therefore, repeated response assessment in good responders will lead to identification of more complete responders. However, no diagnostic test to detect a complete response is entirely accurate and some true complete responses will therefore not be recognized. Fortunately, almost all regrowths that occur in a W&W protocol are salvageable and oncological outcomes are promising.[1,9] In patients with a regrowth, even organ preservation remains possible.[10] Therefore, a repeated response assessment strategy in good responders with delayed or salvage surgery for those who 'fail' is a promising approach.[1,2,11]

Several studies have shown that NOM leads to a higher health-related QoL compared to TME surgery.[12,13] Little is known about the quality of life of those patients who, after an initial W&W approach, eventually require TME surgery. QoL might be impaired because on top of the anticipatory distress, patients who actually develop a regrowth have to undergo the psychological distress of what they feared would happen, bringing extra feelings of uncertainty and fear of death.[14,15] While we likely benefit the good clinical responder group as a whole, do we 'harm' the patients that develop a regrowth from a QoL perspective? The goal of this study was to quantify the possible negative impact on quality of life and feelings of regret and worry for cancer in patients in a W&W program who eventually require TME surgery for a regrowth.

MATERIALS & METHODS

Study Design

This study is part of a multicenter prospective registration study "Wait-and-see" Policy for Complete Responders After Chemoradiotherapy for Rectal Cancer (clin trials gov NCT03426397) and was approved by the institutional review board of our institution. Patients with a complete response after CRTx are included in the study. Patients with a (near) complete response received a repeated response assessment, and all other patients undergo immediate TME surgery (Table S1). Patients who do not develop a clinical complete response after repeated assessments and patients who developed a regrowth later in the follow up undergo delayed TME surgery.

Patient Selection

Patients who received CRTx and TME surgery for adenocarcinoma of the rectum from January 2015–May 2020 were included. Exclusion criteria were delaying surgery for other reasons than regrowth, synchronous metastases, palliative treatment, other malignancy for which active treatment or surveillance. Patients with a local excision as treatment after CRTx were excluded, unless they were followed by a completion TME. Patients who received follow-up elsewhere or were lost to follow-up were excluded. Response assessment was performed 6–8 weeks after the end of CRTx with digital rectal examination, CT-chest and abdomen, pelvic MRI, and endoscopy. Patients with a clinical complete response entered the surveillance program with a three monthly MRI and endoscopy in the first two years as part of the W&W protocol. Patients with a near complete response were restaged after 6 weeks with endoscopy (near complete) and were at that time either included in the W&W protocol, or underwent delayed TME surgery.

Questionnaires

Quality of life was measured by the cancer-specific QLQ-C30 version 3.0 and the colorectal cancer-specific QLQ-CR29. The QLQ-C30 consists of five functional scales, three symptom scales and 6 single items. The 29-item QLQ-CR29 represents an update of the QLQ-CR38. The adapted Dutch version consists out of 4 scales and 17 single items.[16]

The Cancer Worry Scale (CWS) is a validated questionnaire which consists out of four questions evaluating patients' worry for cancer recurrence.[17] The validated Decision Regret Scale (DRS) consists out of 5 questions which assesses regret for a treatment decision.[18] The DRS was used to assess potential regret for choosing a W&W protocol in those patients requiring delayed surgery. The QLQ and CWS questionnaires were distributed by post in June 2020. Non-responders were contacted once by telephone after two weeks. The DRS was obtained by telephone, only in patients who underwent delayed surgery and who had returned the initial questionnaires.

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS version 23.0, Armonk, New York, NY, USA). Patient demographics, number of clinic visits from first presentation until surgery and peri-operative details were obtained from chart review. Follow-up was calculated from the end of CRTx. Scores and missing data of the EORTC questionnaires were handled according to the scoring manual. Higher functional scores indicated increased function, while higher symptom scores represent more severe symptoms. The CWS consists of 4 questions each with a 10-point Likert scale giving a maximum total score of 40. The DRS consists of 5 questions each with a 5-point Likert scale. Scores were handled according to the scoring manual, leading to a percentual score per question. Scores vary between 0–100, where a score >50 signifies a patient having decision regret. All scores were presented as means. To negate the effect of direct postoperative recovery, only questionnaires from patients at least six months postoperatively were included. Wilcoxon rank sum test, Fisher's exact test, linear-by-linear association and general linear models were used to test for differences between groups.

It has been debated how well the QLQ-C30 performs in rectal cancer patients, specifically .[19] The Dutch validation study of the QLQ-CR29 suggested a modification of the original bowel symptom scores, leading to a new subscale with improved scale reliability for Dutch colorectal cancer patients.[16] For these reasons, we performed an exploratory factor analysis (EFA) to expose the latent factors in our dataset which we compared to the QLQ-C30 and CR29 questionnaires. An EFA based on eigenvalues (>1.0) using a Varimax rotation was used. In order not to overestimate effects, an appropriate loading factor of 0.75 was chosen based on our sample size of 51.[20] Internal consistency was assessed by Cronbach's alpha. Construct validity was tested through a 'known groups comparison'; we hypothesized based on literature that patients undergoing APR would have a lower physical functioning score, lower body image, more loss of appetite and more sexual difficulty for men.[21,22]

RESULTS

Patient Demographics & Non-Responder Analysis

Between 2015 and 2020, 94 patients underwent either immediate or delayed TME surgery after CRTx. Eighty-seven patients were eligible for inclusion and were sent the questionnaires by post. Finally, 51 (59%) patients returned three full questionnaire after one follow-up call (Figure 1), 33 who undergone immediate TME surgery and 18 who undergone a delayed TME procedure. Sixteen out of 18 patients returned the DRS questionnaire. Non-responder analysis showed no differences with responders, except for a trend towards more surgical reinterventions in the non-responder group ($p = 0.06$). Five out of these six non-responders underwent immediate surgery (Table S4). There were no significant differences in age, sex, ASA score, cTNM classification, laparoscopy, conversion, readmission, distant relapse and follow up between the immediate and delayed surgery groups (Table 1). The delayed surgery group had significantly more distal tumors ($p = 0.03$), more APR procedures ($p = 0.02$) and more ostomies at time of analysis ($p = 0.02$). Patients in the delayed surgery group had more clinic visits (5 vs. 2, $p < 0.01$).

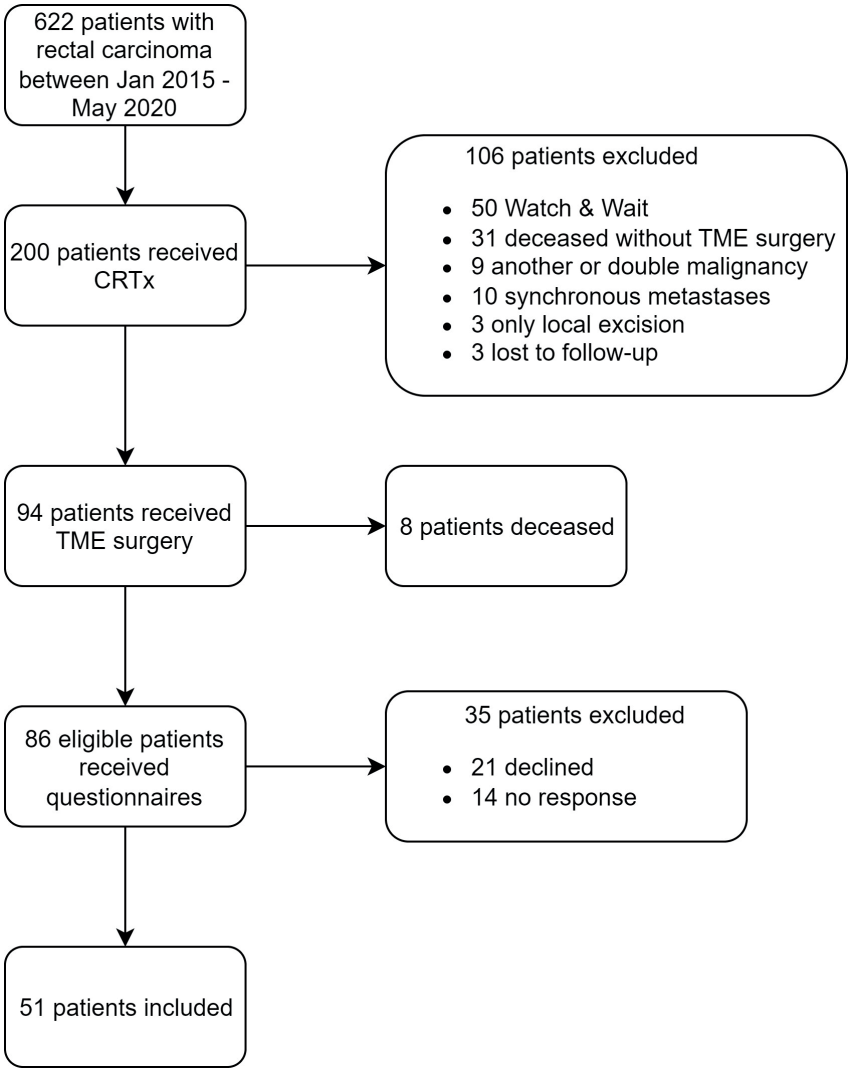


Figure 1 | Inclusion strategy.

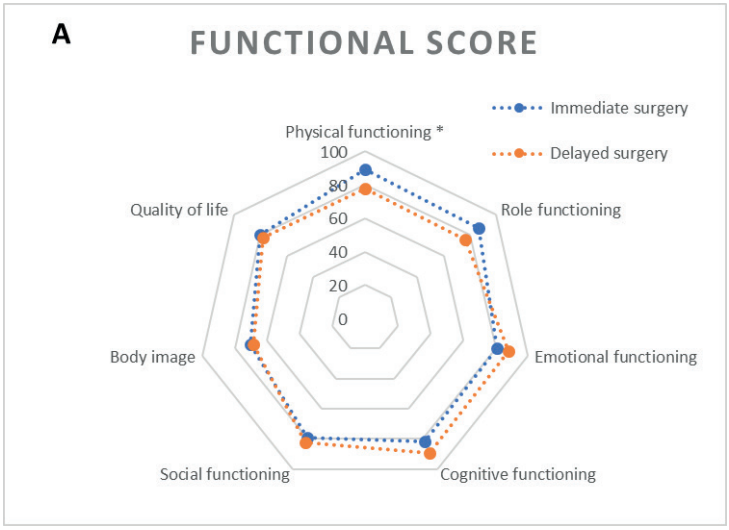
Table 1 | Patient demographics immediate vs. delayed surgery groups. p-(<0.05).

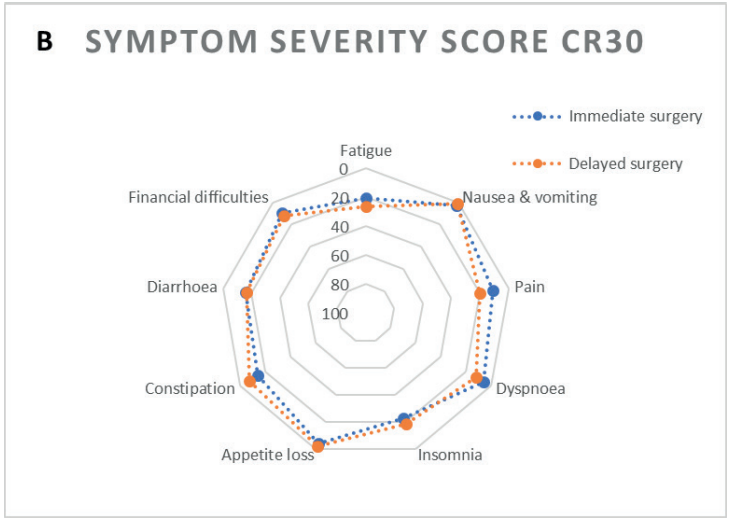
	Immediate Surgery N = 33		Delayed Surgery N = 18		
	N (%)	Mean %	N (%)	Mean	*p*
Age		63.9		61.2	0.33
Sex					
M	17 (51.5%)		11 (61.1%)		0.57
F	16 (48.5%)		7 (38.9%)		
ASAscore					
1	11 (33.3%)		7 (38.9%)		0.74
2	20 (60.6%)		9 (50.0%)		
3	2 (6.1%)		2 (11.1%)		
cT					
3	30 (90.9%)		17 (100%)		0.54
4	3 (9,1%)		0 (0%)		
cN					
0	1 (3.0%)		4 (22.2%)		**0.04**
1	9 (27.3%)		6 (33.3%)		
2	23 (69.7%)		8 (44.4%)		
CRTx interrupted					
0	30 (90.9%)		14 (77.8%)		0.23
1	3 (9.1%)		4 (22.2%)		
Endoscopic distance (cm)		10		6	**0.03**
Time to surgery (weeks)		15		35	**<0.01**
Type of operation					
LAR	24 (72.7%)		7 (38.9%)		**0.02**
APR	9 (27.30%)		11 (61.1%)		
Stoma-free survival					
no stoma	21 (63.6%)		5 (27.8%)		**0.02**
stoma in situ	12 (36.4%)		13 (72.2%)		
Laparoscopy					
no	8 (24.2%)		1 (5.6%)		0.13
yes	25 (75.8%)		17 (94.4%)		
Conversion					
no	28 (84.8%)		17 (94.4%)		0.53
yes	4 (12.1%)		1 (5.6%)		
unknown	1 (3.1%)		0 (0%)		
Readmission					
no	23 (76.7%)		17 (94.4%)		0.23
yes	7 (23.3%)		1 (5.6%)		
Distant relapse					
no	26 (78.8%)		16 (88.9%)		0.46
yes	7 (21.2%)		2 (11.1%)		
Follow up (months)		35		25	0.07

Re:

QLQC30 & CR29

We observed a higher mean physical functioning score (89.2 vs. 77.6, p = 0.03) in the immediate surgery group. When corrected for operation type, no significant difference in mean physical functioning was found (p = 0.25). A non-significant lower mean role functioning score (86.7 vs. 76.2, p = 0.33) was found for the delayed surgery group. The QoL item had a similar mean score (80.5 vs. 78.0, p = 0.52). Arousal for men scored higher in the delayed surgery group (20.0 vs. 57.1, p = 0.02). There was no significant difference between surgical groups in the other function scales. All function and symptom scores are depicted in Figure 2. Tables S2 and S3 show scores for all scales and items.





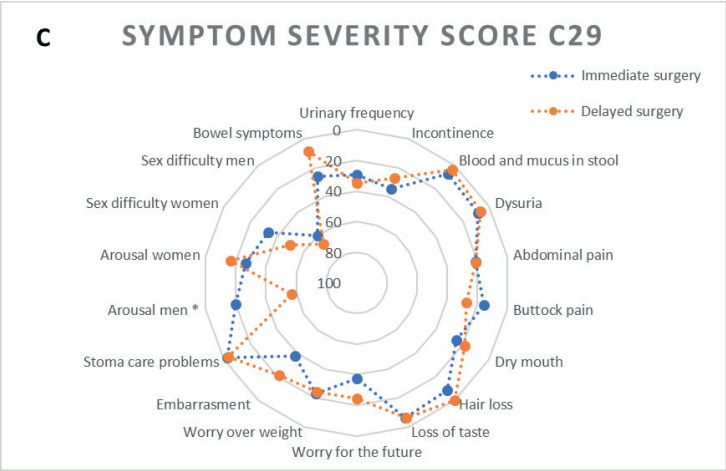
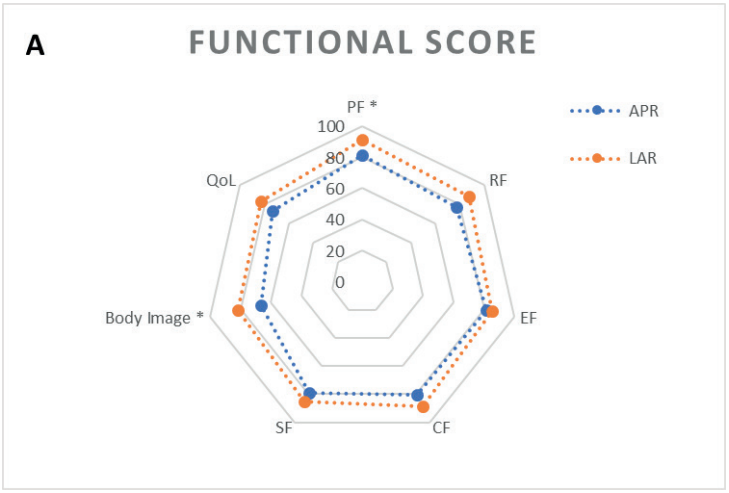


***Figure 2 | Radar charts depicting quality of life for immediate vs. delayed surgery groups. Means** are given. * signifies statistical significance at $p < 0.05$.*
(A) Functional scores and QoL item.
(B) QLQ-C30 symptom scores.
(C) QLQ-CR29 symptom scores.

5

Known Groups Comparison: APR vs. LAR

Mean physical function scale score was lower in patients who underwent APR instead of LAR (77.5 vs. 89.5, $p < 0.01$). No difference was seen between LAR with a deviating stoma and APR for any of the subscales ($p > 0.2$). The APR group had a lower mean body image (66.7 vs. 83.3, $p = 0.03$). Mean symptom score for appetite loss was higher in the APR group (10.5 vs. 2.4, $p = 0.047$). Men in the APR group had a higher mean score for the sexual difficulty symptom item (83.3 vs. 28.6, $p < 0.01$). All scores are shown in Figure 3.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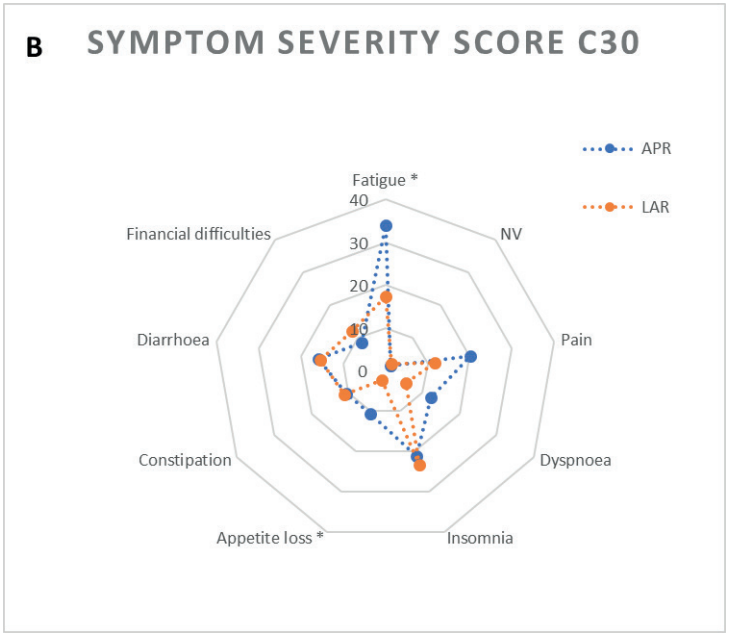
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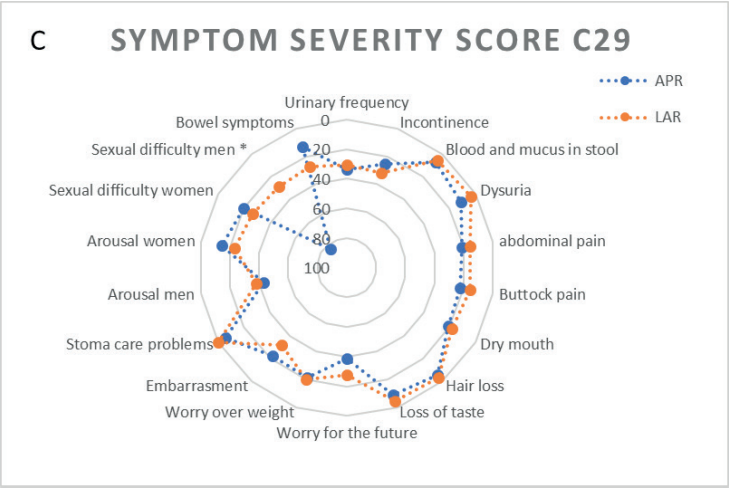

Figure 3 | Radar charts depicting quality of life per operation type. *Means are given. * signifies statistical significance at p < 0.05.*
(A) Functional scores and QoL item.
(B) QLQ-C30 symptom scores.
(C) QLQ-CR29 symptom scores.

5

Cancer Worry Scale

The average CWS score was 14.0 in the immediate surgery group and 10.8 in the delayed surgery group (Table 2, p = 0.21).

Table 2 | CWS score for immediate vs. delayed surgery groups. *Mean + SD are given. Score of >14 indicates high fear of recurrence.*

	Immediate surgery		*Delayed surgery*	
	Mean	*SD*	*Mean*	*SD*
CWS	*14.00*	*9.12*	*10.79*	*7.91*

Decision Regret Scale

Mean item scores varied between 10.7% and 16.1% between items (Table 3). No patient exhibited decision regret for any of the items.

Table 3 | DRS score for delayed surgery group. *Score > 50 indicates decision regret.*

Decision regret scale score (n = 16)		
Item no	Question	Score (%)
1	It was the right decision	12.5
2	I regret the choice that was made	10.7
3	I would go for the same choice if I had to do it over again	14.3
4	The choice did me a lot of harm	14.3
5	The decision was a wise one	16.1

Factor Analysis and Reliability

Exploratory factor analysis revealed six factors within the QLQ C30 explaining 76% of variance, of which the social functioning (Cronbach's α = 0.82) and emotional functioning scale (α = 0.89) were reproduced with good internal consistency. The physical functioning scale (α = 0.79) without 'ADL item' no 5 and the role functioning scale were reproduced together as one factor (α = 0.92). All remaining factors did not form interpretable scales with reliabilities below 0.5.

Factor analysis also revealed six factors within the QLQ CR29 explaining 70% of variance, of which the body image scale (α = 0.85), urinary frequency scale (α = 0.67) and the blood and mucus in stool scale were reproduced (α = 0.50, originally α = 0.56).[16] As in the original Dutch validation study, the original stool frequency scale (α = 0.61) showed greater internal consistency when added to a larger factor including all bowel and stoma problems (items 49–54, α = 0,87).[16] All remaining factors did not form interpretable scales with reliabilities below 0.7. The CWS revealed one underlying factor explaining 70% of variance. Excellent scale reliability was found for the CWS and DRS (α = 0.86 and 0.84, respectively).

DISCUSSION

Patients who undergo delayed TME surgery after CRTX have no impairment of quality of life or more worry for cancer than patients who undergo immediate TME surgery. These patients also exhibit little or no regret of the decision to enter a Watch & Wait protocol. From a quality of life perspective, it seems therefore that a repeated assessment strategy for near complete responders to identify all candidates for a W&W/NOM is not harmful.

QLQ-C30 scores in both groups are in the same range, and comparable to the normal population.[23] Indeed, most studies have found only limited differences between rectal cancer patients and the general population in terms of QoL.[24] It is believed that the experience of going through major surgery and insecurity about cancer, reshapes the patients' perception of life in a positive way resulting in better reported QoL.[25] This so-called 'post traumatic growth' is well documented in (colorectal) cancer patients.[26]

The delayed surgery group does not have a higher score on the CWS, with even a non-significant trend for a lower score (10.8 vs. 14.0, p = 0.2). A cut-off score of 14 on the CWS has been proposed in breast- and colorectal cancer patients to detect high fear of cancer.[27] Patients with an excellent response to CRTx were told to have a favorable prognosis, in addition to he possibility of treatment without surgery. Although eventually requiring a resection, patients might still feel they have a more favorable prognosis. Additionally, patients receiving delayed surgery have had significantly more outpatient clinic visits and examinations. The fact that these patients are in a prospective W&W study with additional counselling and attention, could have resulted in a greater sense of security and less worry for cancer.[28]

Finally, we examined in those patients who underwent delayed surgery if they experienced regret towards the decision to participate. Probably, this is the most discerning indicator from a quality of life perspective. Even though these patients had to undergo delayed surgery, no patients showed decision regret with very low regret scores on all items.

The exploratory factor analysis reproduced most subscales in in the QLQ C-30 and CR-29. The physical functioning scale was reproduced with good internal consistency without the 'ADL' item, similar to a previous validation study.[29] The physical and role functioning scale were reproduced as one factor, suggesting that these questions answered a similar underlying 'functioning parameter' in our subset of patients. Equivalent to the original Dutch validation study, we found moderate scale reliability in the blood and mucus scale and greater internal consistency when all bowel and stoma items were combined in one scale (items 49–54).[16] As reported earlier, our known groups comparison compared well to literature showing good construct validity. Summarizing, the QLQ-CR30 and CR29 showed good validity and was therefore feasible in our sample of neoadjuvant treated rectal cancer patients.

The main limitation of this study is the small sample size. In our watch & wait cohort, only 29 patients required delayed surgery and not all patients participated in the study. Further limitations are the presence of potential confounders and the 59% response rate. There is a higher proportion of patients receiving APR and having a stoma in the delayed surgery group. This could contribute to the non-significant lower mean physical functioning and role functioning score in the delayed surgery group. Patients with a stoma report lower scores on most QoL domains.[30] Moreover, Qol is reportedly higher in patients after LAR compared to APR, although not consistently. The present study showed significantly worse physical functioning, body image, appetite loss and male sexual difficulty after an APR than after a LAR.

The response rate in the present study was 59% and therefore selective non-response might have occurred. Although 59% is below average in surgical postal surveys, surveys in colorectal cancer patients often achieve 50–60% response rates.[31] An RCT in a cohort of 1200 cancer patients investigating response rates showed that the 55% response rate in colorectal cancer is lower than patients with prostate or breast cancer, even after correction for age, sex, marital status, and cancer stage.[32] Our non-responder analysis showed no differences between groups, except for a trend towards more surgical reinterventions in the non-responder group. Furthermore, the temporal variability between date of surgery and completion of the questionnaire is a limitation of this study.

CONCLUSION

In conclusion, there is no impairment of quality of life or more worry for cancer in patients undergoing delayed TME surgery, as compared to immediate TME surgery. Therefore, this study supports a repeated response assessment strategy after CRTx for rectal carcinoma to identify all complete responders from a quality of life perspective.

SUPPLEMENTARY MATERIALS

The following are available online at https://www.mdpi.com/2072-6 694/13/4/742/s1, Table S1: Definition of clinical complete response (cCR) and near cCR. Table S2: QLQ-C30 scores. Table S3 QLQ-CR29 scores. Table S4: Non responder comparison.

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CHAPTER 6

Timing of closure of protective stoma after low-anterior resection for cancer does not appear to affect long-term functional outcome

V.M. Meyer MD, N. Bosch BsC, J.A.G. van der Heijden MD PhD, A.J. Kalkdijk-Dijkstra MSc, J.P.E.N. Pierie MD PhD, G.L. Beets, P.M.A. Broens MD PhD, B.R. Klarenbeek, MD PhD, H.L. van Westreenen MD PhD

Submitted

ABSTRACT

Aim
The aim of this study was to assess the effect of early stoma closure on bowel function after LAR for rectal cancer.

Method
Patients participating in the FORCE-trial who underwent LAR with temporary protective stoma were included in this study. Patients were subdivided into an early closure group (<3 months) and late closure group (>3 months). Endpoints of this study were the Wexner, LARS, EORTC QLQCR29 and FIQL scores at one year.

Results
Between 2017 – 2020, 38 patients had received protective stoma after LAR for rectal cancer and could be included. There was no significant difference in LARS (31 vs 30, p = 0.63) and Wexner score (6.2 vs 5.8, p = 0.77) between the early and late closure group. Time to stoma closure in days was not a predictor for LARS (R2 = 0.001, F (1,36) = 0.049, p = 0.83) or Wexner score (R2 = 0.008, F (1,36) = 0.287, p = 0.60) after restored continuity. There was no significant difference between any of the FIQL domains of lifestyle, coping, depression and embarrassment. In the EORTC QLQ-29, body image scored higher in the late closure group (21.3 vs 1.6, p = 0.004).

Conclusion
Timing of stoma closure does not appear to affect long term bowel function and quality of life. To improve functional outcome, attention should be focused on other contributing factors.

Key words
rectal cancer; stoma closure; low anterior resection; quality of life; anorectal function

INTRODUCTION

TME surgery is the gold standard for resection of rectal carcinoma, leading to significant improvement in survival since its introduction by Heald.[1] Sphincter preserving techniques are preferred to avoid permanent stoma creation, something that is highly valued by patients.[2] However, the majority of patients suffer from impaired bowel function after low anterior resection (LAR).[3,4] As a consequence of improved cancer treatment, functional outcome is very important for long-term rectal cancer survivors.[5]

Anastomotic leakage is a major complication after LAR and therefore a protective stoma is commonly used to prevent complications of an anastomotic leakage. Although a protective stoma will lead to a reduced rate of re-operation in case of a leakage, stoma related morbidity such as dermatitis, high output and/or herniation occurring in up to 35% of patients needs to be taken into account.[6–8] Also, protective stoma after LAR can contribute to a pathological microbiome, atrophy of the bowel wall musculature and impaired mucosal absorptive function distally which all could affect bowel function after stoma closure.[9–13] Thus, early closure of a stoma could be beneficial. However, there are several reasons why there is no clear consensus on the optimal timing of temporary stoma closure after LAR.[12–14] For example, most cohort studies do no express clear guidelines on timing of stoma closure and randomized trials reporting on timing of closure are not powered for this outcome. Moreover, the decision to create a stoma is often left to the surgeon (i.e., more difficult cases) and often the effect of patient related factors is not reported.[15,16]

Furthermore, a potential difference in functional outcome is difficult to investigate because several scoring systems are used to evaluate bowel function. Most frequently used after LAR is the LAR score, which is limited because it does not incorporate QoL or differentiate between incontinence and obstipation related symptoms.[17,18] In an attempt to capture the full extent of bowel related problems, other frequently used validated bowel function and health related quality of life (HRQoL) scores are being used such as the Fecal Incontinence Quality of Life (FIQL) scale, Wexner incontinence score and the EORTC QLQ CR-29 questionnaire. These questionnaires are designed for different populations, answer different questions and possess different validated psychometric properties while being used interchangeable, making comparison of studies difficult.

The aim of this study is to assess the effect of early stoma closure on bowel function after LAR for rectal cancer.

METHODS

The FORCE trial was designed as a multicenter two-armed randomized controlled trial comparing the effect of pelvic floor rehabilitation (PFR) on functional outcome after rectal resection.[19] Patients participating in the FORCE-trial who underwent LAR with temporary protective stoma were included in this study. Endpoints of this study were Wexner, LARS, EORTC QLQ-CR29 and FIQL scores at one year. For this study, patients were divided into two groups based on the timing of stoma closure. In the Netherlands, closure of a temporary stoma after uncomplicated rectal resection is generally planned 8-12 weeks after LAR. Patients who underwent stoma closure within 3 months were defined as the 'early' closure

group. Patients in the 'late' closure group had their stoma closed after 3 months. Furthermore, a sub analysis of 'very late' closure group after 6 months and pelvic floor rehabilitation group was performed. Eligible patients underwent LAR for rectal cancer and were 18 years or older. Those with comorbidities such as inflammatory bowel disease or proctitis, a short life expectancy (<1 year), locally advanced tumors which required extensive resections and those who had participated in biofeedback therapy in the last six months before the LAR procedure were excluded. The FORCE trial was approved by the Ethics Committee in Arnhem/Nijmegen, the Netherlands (reference number NL59799.091.16).

Patients

This study was conducted in 2 academic and 15 teaching hospitals in the Netherlands between October 2017 and March 2020. Patients were asked to fill in the questionnaires one year after stoma closure. Demographic details, tumor characteristics, use of neo-adjuvant treatment, perioperative records including complications and relevant history were registered prospectively. All patients provided written and verbal informed consent.

Questionnaires

Functional outcome was measured through the DeFec questionnaire which contains four validated questionnaires: the LARS and Wexner incontinence score for bowel function and HRQoL through the FIQL and EORTC QLQ-CR29 questionnaires.[20] A multimodality approach was chosen; patients could fill in their questionnaires online or via mail. Patients were solicited through telephone calls in case of non-response.

The validated Wexner incontinence score ranges from 0-20. Wexner scores ≥ 1 were considered to be symptomatic (1-4: mild incontinence, 5-8: moderate incontinence, 9-20: severe incontinence). A clinically relevant difference was defined as minimally two points.[21]

The validated Fecal Incontinence related Quality of Life score is composed of a total of 29 items; these items form four scales: Lifestyle (10 items), Coping/Behaviour (9 items), Depression/ Self-Perception (7 items), and Embarrassment (3 items). A FIQL score of 1-4 represents poor to good QoL.

A value of 0.4 was considered the minimal important change (MIC) for the FIQL in our sample.[22]

The frequently validated LARS score consists of 5 subscales which amount to a score of 0-42 points. LARS score is divided into clinically significant subgroups of no LARS (0-20), minor LARS (21-29) and major LARS (30-42).[23]

The validated EORTC QLQ-CR29 is a tumour specific HRQoL questionnaire for colorectal cancer patients. It consists of four scales and 19 individual items in Dutch and has been validated in neoadjuvant treated rectal cancer patients.[24] The diverse function and symptom scales range from 0-100, of which a higher function scores resembles a better outcome and where a higher symptom score represents more complaints.

Statistical analysis

Descriptive statistics were obtained to identify any outliers and determine distribution of data. If the assumptions for parametric testing were violated, a non-parametric alternative was used. Mean change in continuous data scores were compared using an analysis of variance (ANOVA). For categorical data, Chi-square or Mann-Whitney U test was used. Fishers exact test was used in case of small numbers (<5). Categorical ordered data (such as the Wexner and LARS scores) were compared using the Jonckheere-Terpstra test for ordered alternatives. A linear regression model with time to stoma closure was fitted to predict bowel function (LARS and Wexner score). Time to stoma closure was defined as the number of days between index surgery and stoma closure. Analysis with correction of possible confounding factors was performed using ANCOVA. All (possible explanatory) variables that were different ($p < 0.1$) between the early and late closure group were included in multivariable analysis. Data was statistically significant at $p < 0.05$. All questionnaires were handled according to their manuals. IBM SPSS 23 was used.[25]

RESULTS

Patient related outcomes

Between October 2017 and March 2020, 106 patients were included in the FORCE trial. Fifty-seven patients underwent LAR without stoma and the remaining 49 patients were eligible for this study.

Forty-nine patients had received a protective stoma of which eight patients developed progression of disease, two patients withdrew due to personal circumstances and one patient withdrew due to nononcological co-morbidity and were therefore excluded. Finally, 38 patients with a protective stoma returning full questionnaires at one year follow-up were included (Figure 1). Response rate of participating patients, measured after inclusion and randomization, was 91%.

There were no differences in age, sex, BMI, ASA score, cTNM classification, distance from anal verge, use of neo-adjuvant therapy, pelvic floor rehabilitation, length of stay, complications or comorbidities for both groups (Table 1). There was a trend towards more surgical reinterventions after LAR in the late closure group ($0.05 < p < 0.1$). Four patients had received their stoma later than index surgery due to complications.

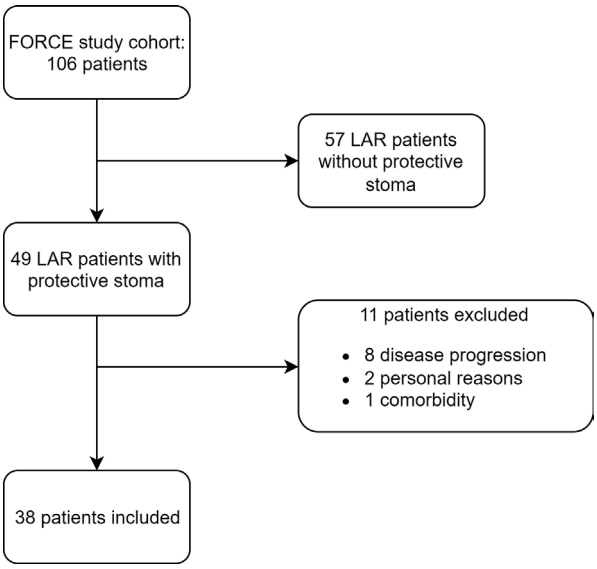

Figure 1 | PRISMA flow-chart of patient inclusion.

Table 1 | Patient related and peri-operative factors. *P in italic if >0.05 <0.10. SCRT = short-course radiotherapy. CRTx = chemoradiotherapy.*

		Stoma closure				
		< 3 months 14 patients		>3 months 24 patients		
		Mean*	Count	Mean*	Count	p value
Age		60		60		0.93
Gender	male		11		15	0.47
	female		3		9	
BMI		27.3		26.5		0.61
ASA classification	ASA 1		4		8	0.76
	ASA 2		7		13	
	ASA 3		3		3	
Tumor Height (cm)		6.7		6.4		0.71
TNM cT-stadia	cT1		1		1	0.80
	cT2		3		7	
	cT3		10		15	

TNM cN-stadia	cN0		7		8	0.40
	cN1		3		10	
	cN2		4		5	
TNM cM-stadia	cM0		14		19	0.26
	cM1		0		3	
	cMx		0		1	
Neo-adjuvant therapy	yes		10		17	0.94
	no		4		7	
Type of surgery	laparoscopic		12		14	0.19
	robot		2		8	
	conversion		0		2	
Pelvic floor rehabilitation	yes		7		10	0.38
	no		7		14	
Time to closure in days (median)		67		139		
Length of stay in days		7		10		0.24
Blood loss during surgery in cc		34		67		0.26
Surgical reintervention	Yes		0		6	*0.07*
	no		14		17	
Radiological intervention	Yes		0		1	1.0
	no		14		22	

[*] *Median reported for 'time to stoma closure' due to no Gaussian distribution.*

Bowel function & Health related Quality of Life

There was no significant difference in LARS (31 vs 30, p = 0.63) and Wexner score (6.2 vs 5.8, p = 0.77) between the early and late closure group. Prevalence of major LARS and categorical Wexner score were not statistically different between groups (Table 1). Linear regression analysis did not reveal time to stoma closure as predictors for LARS (R2 = 0.001, F (1,36) = 0.049, p = 0.83) or Wexner score (R2 = 0.008, F (1,36) = 0.287, p = 0.60) after restored continuity. There was no significant difference between any of the FIQL domains of lifestyle, coping, depression and embarrassment (Table 1). In the EORTC QLQ-29, body image scored higher in the late closure group (21.3 vs 1.6, p = 0.004) (Figure 2). Body image in the late closure group

remained significantly higher in multivariable analysis after correction for anastomotic leak, operating time, complications after surgery, length of stay and M1 disease (p = 0.02). There was no significant difference between the other items of the QLQ-29 (Figure 2).
Subanalysis of groups with and without PFR both did not show a significant difference between early and late closure for mean Wexner score (p = 0.49 and 0.97), LARS score (p = 0.36 and 0.59) or any of the FIQL and CR-29 domains. For the group of patients with very late closure (defined as > 6 months), we found no significant differences for LARS (p = 0.58), Wexner (p = 0.28) or any of the Qol (FIQL and CR-29) domains (p > 0.4) in 10 patients. Three of these patients received PFR. Patients undergoing stoma closure after 6 months had significantly more anastomotic leaks (p < 0.001), admission days (p < 0.001) and a trend towards more postoperative complications at index surgery (p = 0.08). There was no significant difference in LARS (p = 0.73), Wexner (p = 0.53) or any of the FIQL domains (p >0.75) between 7 patients requiring a reintervention and 31 patients who did not. No patients died.

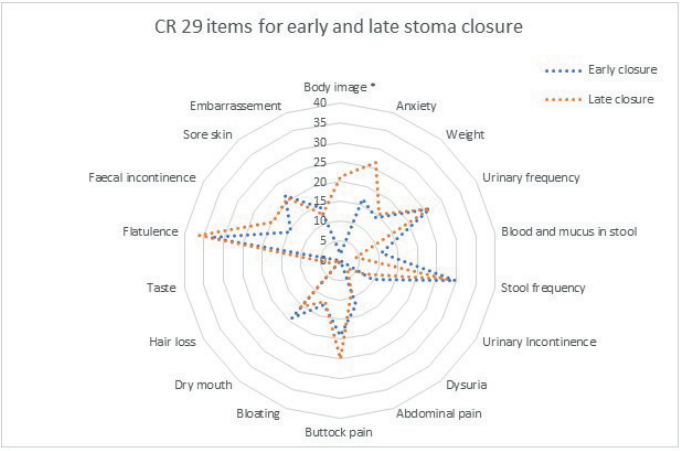

Figure 2 | CR 29 item scores for early closure (<3months) and late closure (>3 months) groups at one year.
* denotes significance at p < 0.05

Table 2 | Functional outcome parameters and one year after stoma closure.

		Functional outcome 1 year after stoma closure				
		< 3months 14 patients		>3 months 24 patients		
		Mean	Count	Mean	Count	p-value
LARS score		31		30		0.63
LARS cat	No or minor		4		12	0.31
	Major		10		12	
FIQoL	Lifestyle	2.51		2.78		0.46
	Coping	2.18		2.33		0.68
	Depression	2.56		2.66		0.79
	Embarrassment	2.48		2.46		0.97
Wexner		6		6		0.76
Wexner cat	No symptoms		0		2	0.60
	Mild		7		8	
	Moderate		3		8	
	Severe		4		6	

Cat = categorical

DISCUSSION

Stoma closure within 3 months does not appear to improve long-term bowel function or HRQoL, as measured by the Wexner, LARS, QLQ CR-29 and FIQL scores.

In this study, we did not find a significant correlation between time to stoma closure and LARS or Wexner score. Literature on this subject is scarce, hindering a proper comparison of studies.[15] The latest review on the subject by Podda et al. including 7 RCT's could not find a difference in LARS between early (<30 days) vs late (>60 days) stoma closure.[26] Vogel et al. performed an extensive pooled analysis of 719 patients including 4 RCT's comparing early versus late closure and found a mean difference in closure time of 2.39 months between no and major LARS groups (95% CI, 1.28–3.51, $p < 0.0001$: $I2 = 21\%$,$X2 = 0.28$).[27] However, median

time to closure varied from 2.4 to 15.6 months. In their comprehensive review, a proposition for timing of stoma closure could not be provided. They also reported that 5 out of 6 included studies did not find a significant association between LARS and timing of closure.[27]

Observing the high variability in interval to stoma closure, a sub analysis for interval > 6 months was performed in which we found no significant differences for LARS, Wexner, FIQL and CR-29 scores in 10 patients. Hughes et al. showed that stoma closure within 6 months is protective for major LARS (OR 0.2, 95% CI, 0.1–0.3, $p < 0.01$) and after 1 year it becomes associated with major LARS (OR 3.7, CI 95%, 1.1–13.1, $p = 0.03$). Obviously, such late closure of a diverting ostomy is often related to a complicated clinical course which could influence functional outcome.[28,29] In our series more anastomotic leaks, admission days and a trend towards more postoperative complications were found in patients who underwent stoma closure >6 months. Although small sample size prohibited a formal analysis, worse functional outcome after 'very' late closure could very well represent an anastomosis related complication rather than an effect of timing of stoma closure.

Although no difference in bowel function was found between early and late groups, body image was significantly better in the late closure group. This result appears to be in line with a secondary analysis of the EASY study that examined health-related quality of life (HRQOL) following early versus late closure of a temporary ileostomy. This study also showed improved QoL parameters (less bodily pain with increased mental health at 12 months, $p < 0.05$ for both) for their late closure group.[30] It has been shown that patients dealing with chronic conditions and cancer appear to reset internal values and even report higher QoL than their healthy peers. This so-called 'response shift' illustrates a change in perspective on life and is common in colorectal cancer survivors. [4,31] Thus, the observed improved QoL properties in patients undergoing late closure (often due to complications) could be explained by a more pronounced response shift in this particular group of patients.

A limitation is the sample size of this study, prohibiting more extensive analysis. Like most studies reporting on timing of stoma closure, the FORCE trial was not powered for this outcome making our study theoretically more susceptible to falsely accepting that timing of stoma closure does not affect outcome (type 2 error). Also, the study protocol did not include data on morbidity of stoma closure.

The decision to create a stoma was a pragmatic approach of the surgeon ensuring optimal treatment for the individual patient, but could introduce selection bias. In the late closure group, there was a trend towards more anastomotic leakage, which could have impacted functional outcome.

There are many factors that impact on functional outcome. Coping mechanisms, response shift and low anastomoses, radiotherapy and anastomotic leakage will influence the perceived bowel function.[14,31–33] Timing of stoma closure could be a contributing factor, but is probably not a highly important one. Other factors such as dose adjustment and more fractioning of radiotherapy has shown to improve functional outcome.[34–36] Furthermore, organ sparing treatment (when possible) will lead to a better functional result then resection.[37] Also, there are indications that bowel dysfunction after stoma closure could be temporary.[18,27] For example, Gadan et al. found in a 12-year follow-up of their RCT comparing anorectal function

after protective stoma that there was no difference in categorical LARS incidence, but specific symptoms did occur more often in temporary ostomates.[10] And finally, the stoma itself appears to be a more important factor than timing of closure. Vogel et al. showed in their review of 7 studies that major LARS occurred 2.84 times more often in patients with a stoma. Up to 9% of patients develop a serious complication following stoma closure requiring re-operation or ICU, one in five is readmitted within 30 days of stoma creation and, often underreported, up to 35% of patients develop an incisional hernia after stoma reversal of which two thirds require a re-operation. This had led to a change in strategy towards highly selective use of protective stoma combined with pro-active leakage management in certain centers who now report a high bowel continuity rate and lower readmission rates without increased leakage, re-operation or mortality.[40–42] This suggests that a standard diverting ostomy is perhaps not the risk adverse strategy we once thought, but maybe should be reserved for a selected group of patients.[40]

The GRECCAR-17 trial, comparing quality of life between selective vs standard use of diverting ostomy after LAR for cancer, is now underway.[43] Overall, attention should be focused on other contributing factors then timing of stoma closure to improve functional outcome after LAR for rectal cancer.

CONCLUSION

Timing of stoma closure does not appear an important factor in long term bowel function and HRQoL. To improve functional outcome, attention should be focused on other contributing factors.

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PART III

Survey response assessment

CHAPTER 7

Global overview of response rates in patient and health care professional surveys in surgery

Vincent Maurice Meyer, MD, Stan Benjamens, Bsc, Mostafa El Moumni, MD, PhD, Johan F.M. Lange, MD, PhD, Robert A. Pol, MD, PhD

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ABSTRACT

Objective
Identify key demographic factors and modes of follow-up in surgical survey response. Surveys are widely used in surgery to assess patient and procedural outcomes, but response rates vary widely which compromises study quality. Currently there is no consensus as to what the average response rate is and which factors are associated with higher response rates.

Methods
The National Library of Medicine (MEDLINE/PubMed) was systematically searched from Januray 1, 2007 until February 1, 2020 using the following strategy: (((questionnaire) OR survey) AND "response rate") AND (surgery OR surgical). Original survey studies from surgical(-related) fields reporting on response rate were included. Through one-way analysis of variance we present mean response rate per survey mode over time, number of additional contacts, country of origin, and type of interviewee.

Results
The average response is 70% over 811 studies in patients and 53% over 1746 doctor surveys. In-person surveys yield an average 76% response rate, followed by postal (65%) and online (46% web-based vs 51% email) surveys. Patients respond significantly more often than doctors to surveys by mail ($P < 0.001$), email ($P < 0.003$), web-based surveys ($P < 0.001$) and mixed mode surveys ($P < 0.006$). Additional contacts significantly improve response rate in email ($P < 0.26$) and web-based (P ¼ 0.041) surveys in doctors. Awide variation in response rates was identified between countries.

Conclusions
Every survey is unique, but the main commonality between studies is response rate. Response rates appear to be highly dependent on type of survey, follow-up, geography, and interviewee type.

Keywords
email, postal, questionnaire, response rate, survey, telephone

INTRODUCTION

Surveys are often conducted in the field of surgery, where they represent a valuable means of gaining insight into a topic of interest (operative technique, quality of life, complications, expert opinion) from a wide-ranging selection of people (surgeons, patients, residents, students). This robust sampling method provides useful information when the sample selected is representative of the population and its design reliable, unbiased, and discriminatory.[1–3]

The quality of a survey is mostly threatened by a lack of response (nonresponse bias, incomplete questionnaires) or an undesired response (social desirability bias, poor test-retest reliability, satisficing). Significant research has been done on the latter by Krosnick, who introduced the theory of "satisficing" in survey methodology.[4] Krosnick states that it involves a significant amount of cognitive work to select the optimal answer to a question and (some) respondents would want to minimize that burden. Weak or strong satisficing, a portmanteau of satisfy and suffice, then reflects the act of shortcutting cognitive processes to alleviate the burden of choosing. The respondent answers the questions at hand sufficiently, but with the least effort. This will manifest in selecting "don't know" options, random answers, and socially desirable answer options. The degree of satisficing depends on the motivation of the respondent and task difficulty.[5]

In the lack of response, the items themselves are hugely important; shorter questions and surveys, engagement to the subject, personalization of the questionnaire, and yes/no questions will attribute to a higher response rate.[6–9] Survey mode, number and type of follow up, type of interviewee, and geographic variance also significantly impact response rate.[10–13]

These measurable aspects of response rate comprise a considerable, but only a part, of the puzzle. A low participation rate will introduce nonresponder selection bias (random sampling variability), which impairs validity of the researchers' results and as such is often noted as a study weakness by peer reviewers.[3,14]

A tremendous effort is therefore made toward increasing response rates to surveys. A 2009 Cochrane systematic review examined 121 different strategies to improve response rate in 481 postal and 32 electronic surveys showing that a monetary incentive, personalization, and shortening of the survey improves response rate.[15,16] However, it does not state what a "good" or "acceptable" response rate is. Although often critiqued and with >500 studies reporting on interventions to enhance response rates, we still lack a consensus as to what an ideal or even average response rate is.[1,17–19]

Through a global systematic review of the literature we aim to provide objective data on response rates in survey studies in the field of surgery. We will present the average response rate per type of survey and follow-up, country, and type of interviewee thereby providing researchers with a tool for individual study design.

MATERIALS AND METHODS

Search Strategy

Data collection and analysis were performed according to the Preferred Reporting Items for Systematic Reviews andMeta-Analyses (PRISMA) statement.[20] The National Library of Medicine (MEDLINE/ PubMed) was systematically searched from January 1, 2017 until February 1, 2020 as follows: (((questionnaire) OR survey) AND "response rate") AND (surgery OR surgical). The review process was discussed in detail with all authors beforehand. Studies were independently screened by 2 authors (V.M. and S.B.). Studies were marked if one of the authors doubted suitability and were subsequently checked by the first author to ensure uniformreporting. In case of disagreement, consensus was reached through discussion with all authors.

Studies reporting in English on response rates to questionnaires in surgical and surgery-related fields of medicinewere included.When studies reported response rates on multiple types of interviewees or modes of survey, these sub results were included separately. Studies reporting multiple surveys over time were excluded due to possible bias. Reviews, conference abstracts, case reports, and studies reporting solely from nonsurgical (or related) fields of medicine, paramedicine, or nursing were also excluded. Primary end point was mean response rate per type of survey. Secondary outcomes were response rate over time and per type of follow up, country of origin, and type of subject. Subjects were either patients or health care professionals (doctors). All identified articles were extracted to an Excel sheet in a predefined format containing Pubmed ID, title, authors, country, field of surgery, no. of interviewees that responded, response rate, no of interventions, type of interventions, mandatory nature, and responder reward. Surveys were divided in person (face to face or telephone), postal, email, or web-based surveys in case of an online questionnaire. The miscellaneous group entails mixed-mode surveys.

Follow-up was recorded as none, once, twice or >3. Follow-up could consist of a different mode of survey, that is, a telephone call after a letter was sent. Data were analyzed using IBM Statistics software SPSS 19 (2010).[21] Descriptive statistics were obtained. Student t test was used to compare between health care professionals and patients. One-way analysis of variance analysis was performed for response rate over time and per follow-up contact. Countries with <10 survey studies were grouped under continent.

RESULTS

Literature Search

The initial search resulted in 5693 potential studies. After screening of the abstracts 1435 articles were excluded, leaving 4258 articles for full-text assessment. After a detailed examination, 1679 articles were excluded for various reasons (see online supplement PRISMA Flow Chart, http://links.lww.com/SLA/C247). The final selection yielded 2579 surveys matching the inclusion criteria.

Response Rates Relative to Type of Survey

The average response rate of the 2579 included studies is 58.6% ± 24.0% (mean ± SD), which is 70.0% ± 18.4% over 811 studies in patients and 53.3% ± 24.5% over 1746 health care professionals' surveys.

Figure 1 shows the average response rate per mode of survey of patients and health care professionals. In-person studies yielded the highest average response rate: 77.8% ± 18.0% and 74.5% ± 18.7% for patients and health care professionals, respectively. Postal studies average a 68.0% ± 17.0% and 60.4% ± 18.1% response rate. Email studies give an average response rate of 68.0% ± 17.1% for patients and 50.5% ± 23.3% for health care professionals. Webbased surveys offer an average response rate of 59.3% ± 18.9% and 45.8% ± 25.0% for patients and health care professionals, respectively. In the mixed methods group the average response rate for patients is 68.7% ± 20.0% and for health care professionals 62.0% ± 23.0%.

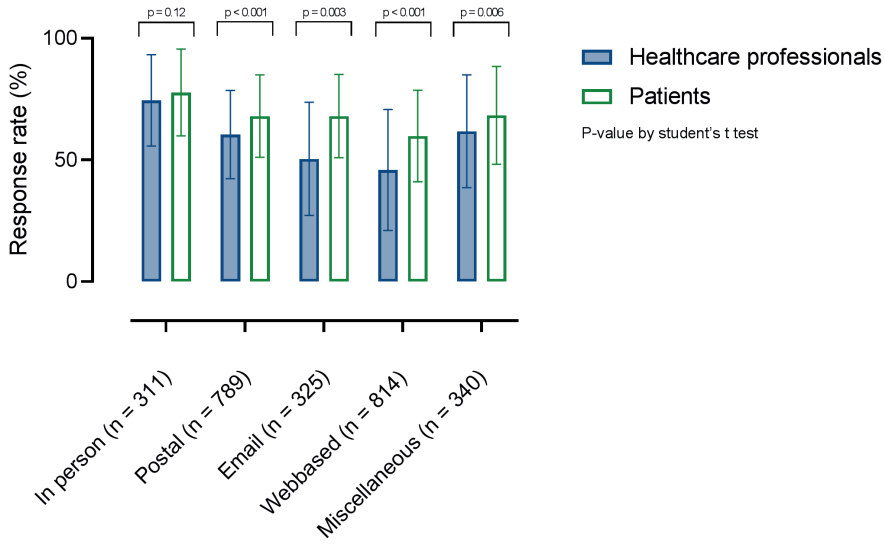

Figure 1 | Mean response rate and standard deviation per mode of survey for patients and healthcare professionals.

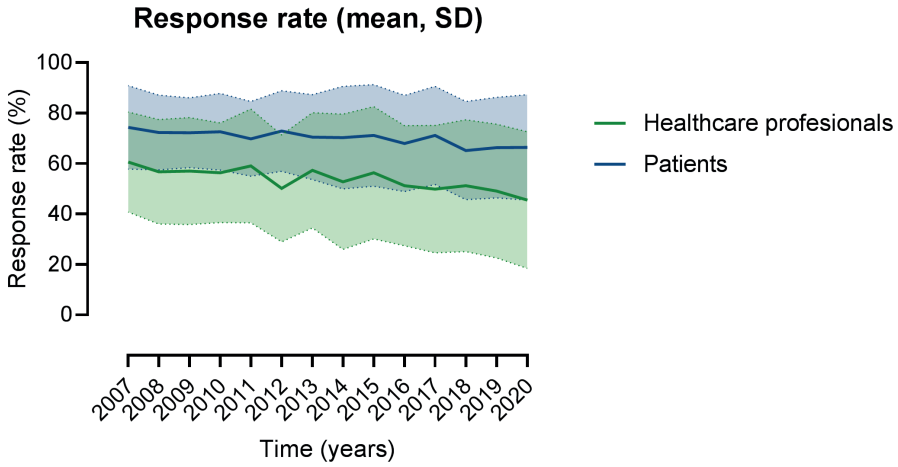

Figure 2 | Response rate per type of interviewee (patient or health care professional) over a thirteen-year interval.

No statistically significant difference in response rate between health care professionals and patients was found in "in person" surveys (P = 0.12). Patients respond significantly more often than health care professionals to surveys by mail (P<0.001), Email (P<0.003), webbased surveys (P<0.001), and mixed mode surveys (P<0.006). This effect is consistent over the whole study inclusion period (Figure 2).

Response Rates Relative to Follow-Up

Figures 3 and 4 show the response rate per mode of survey according to number of interventions, for patients and health care professionals, respectively. The Email and web-based surveys are mostly directed at health care professionals (312 vs 789 studies, respectively) and less at patients (13 vs 30 studies). Additional contacts significantly improve response rate in email (P = 0.26) and web-based (P = 0.041) surveys in health care professionals. A similar trend is seen for 1 and 2 follow-up contacts in email and web-based studies in patients, although overall follow-up is not statistically significant in the Email (P = 0.22) and web-based (P = 0.46) group. Online surveys with follow-up are not often used for patients (3 Email and 15 web-based studies). Follow-up has a significant negative effect in "in person" studies (P = 0.013), where sample size is also small for ≥ 2 follow-up contacts (8 studies).

For the survey studies distributing questionnaires to patients by person (P = 0.76) or by mail (P = 0.65) and for surveys given to health care professionals by mail (P = 0.936), there is no significant difference in response rate with or without follow-up.

Geographical Differences

Figure 5 shows response rates (mean, SD) per country of origin. Patients partake more often than health care professionals in survey studies around the world.

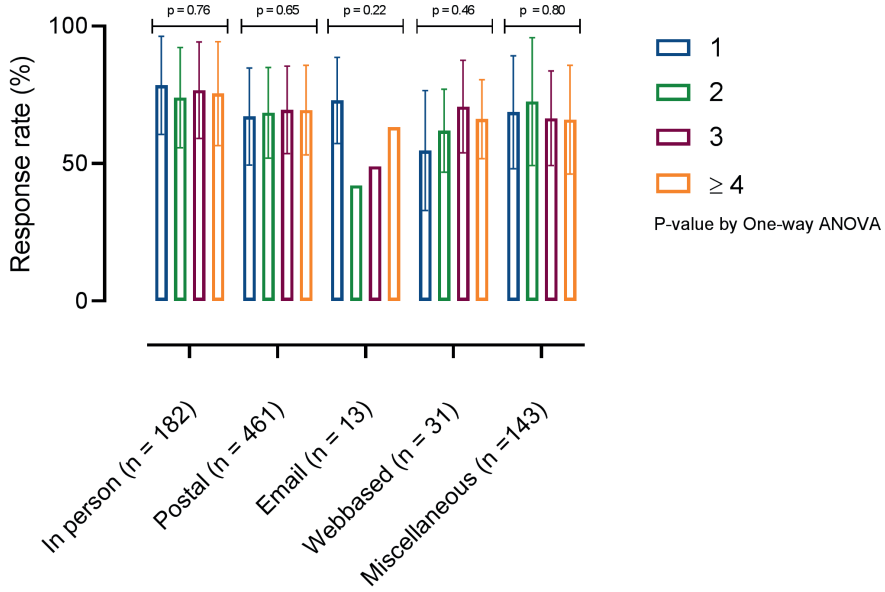

Figure 3 | Response rate per number of contacts per mode of survey for patients.

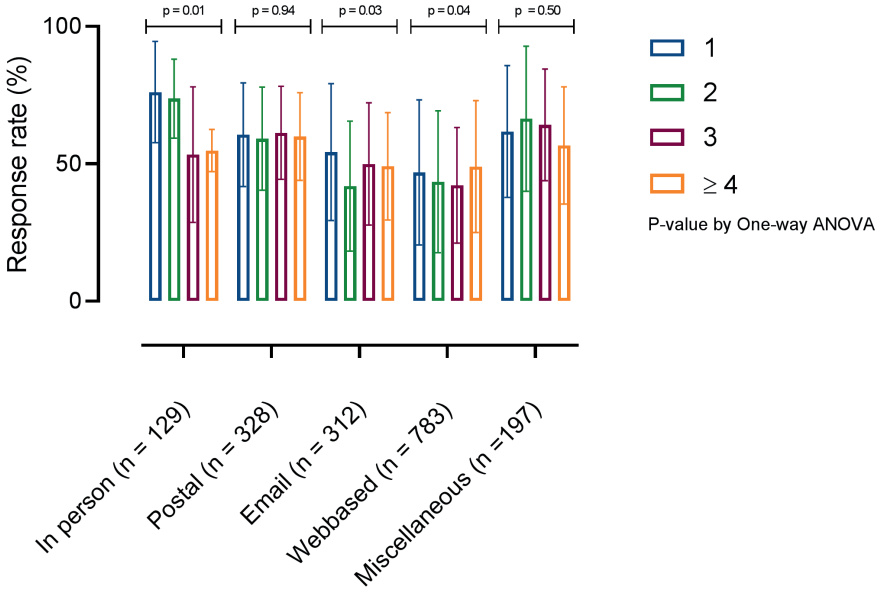

Figure 4 | Response rate per number of contacts per mode of survey for healthcare professionals.

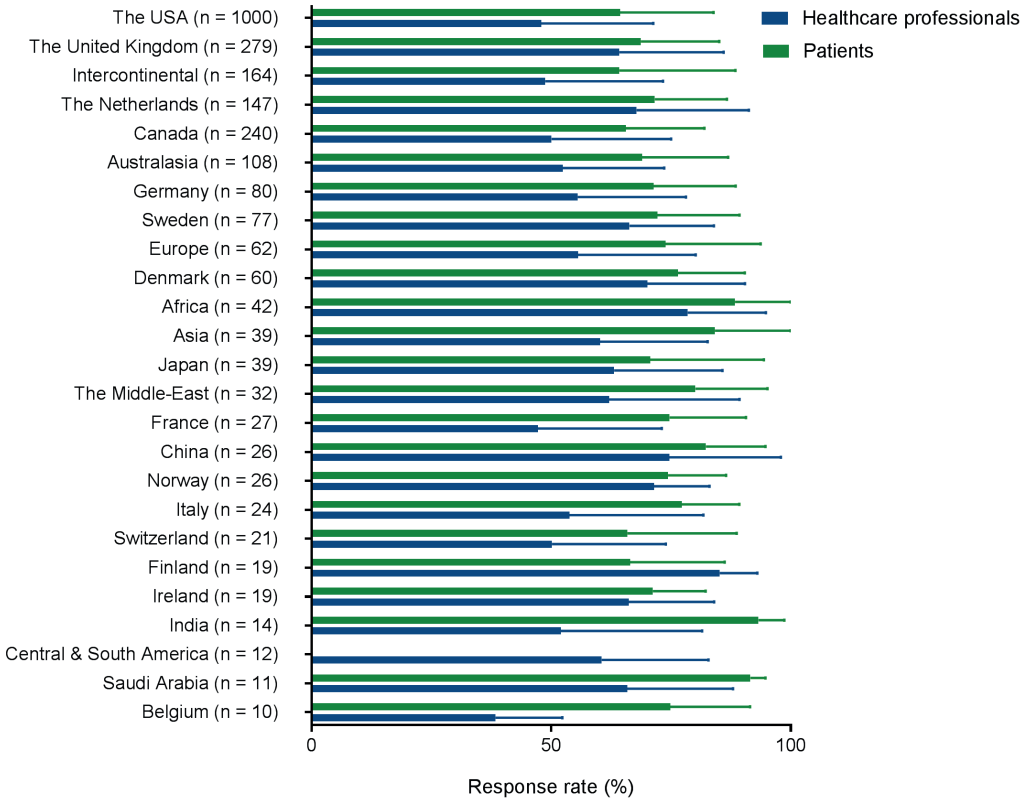

Figure 5 | Response rate and standard deviation per country, region, or continent of origin.

The high patient response rate in Africa (88.1% ± 12.0%), Asia (83.9% ± 16.4%), Middle-East (80.1% ± 15.0%), China (82.3% ± 12.4%), India (93.3% ± 5.4%), and Saudi-Arabia (89.4%) reflects solely postal and in-person questionnaires. The United States has the lowest average respondent score over 225 patient surveys (64.2% ± 19.5%), with a high proportion of Email and web-based studies.

The highest response rates for health care professionals were found in Finland (85.2% ± 7.9%), Africa (77.5% ± 16.0%), China (74.7% ± 23.3%) and Norway (71.5% ± 11.6%), with only Norway reporting on Email and web-based surveys. Lowest response rates for health care professionals are found in Belgium (38.4% ± 14.0%), France (47.3% ± 25.8%), United States (48.0% ± 23.3%), and Intercontinental studies (48.8% ± 24.9%). Intercontinental studies (91%), Belgium (80%), United States (78%), and France (57%), mainly report email and webbased studies.

DISCUSSION

Our analysis is a global representation of survey studies in the surgical field and the largest systematic review to date in this field. We found an average response rate of 70.0% ± 18.4% (mean ± SD) in 811 patient surveys and 53.3% 24.5% in 1746 health care professional surveys. Health care professionals were found to have lower response rates, which has been reported before.[12,22–24] Our review confirms that health care professionals participate less often in postal and online surveys than patients do, which is consistent over time. Health care professionals are probably a very specific group prone to satisficing, where time spent and a lack of benefit are key factors. Lowering both effort and time can be achieved in a variety of ways such as shortening a survey, shortening the questions or offering yes/no options, allowing the health care professional to decide when to fill it in (postal vs face to face), pre-stamping the return envelope, and/or providing an online survey option.[12,22]

Our analyses show that in-person surveys yield an average 76% response rate, where postal (65%) and online (46% webbased vs 51% email) survey response is lower on average. We therefore suggest to appraise response rate on type of survey, that is, a 65% response rate in an in-person survey represents a below average statistic for reviewers. However, a 65% response rate in a postal study parallels the average for that type of survey and should be aimed for when attempting a postal survey.

These results are in line with studies from other nonsurgical medical fields where usually a higher response rate is reported for inperson versus postal and for postal versus online surveys.[11,13,25–26]

Real-time data tracking, immediate survey delivery, and low costs have led to a rise in online surveys, but response rates tend to be lower and methodologies questionable.[27,28] Nowadays, with the general overflow of Email contact, respondents' willingness to partake in email surveys or satisficing could be negatively affected. It is a general consensus that a more personal face-to-face or telephone interview will reach a higher response rate, but such surveys weigh more heavily on time and resources.[15,17,18,26,9–31]

Additional contacts are frequently used to generate a higher response rate. Extensive research by Dillman et al has shown that great administrative detail for survey personalization, including additional mailing, boosts response rates.[7,32–40] Our study shows that additional contacts do not significantly raise response rates compared to a single questionnaire in postal and in-person surveys, contradicting the findings of Dillman et al.[27] This difference could be explained by a general trend of declining response rates around the turn of the century.[10,41–43] The method used by Dillman et al, however, encompasses more than just a reminder letter. The total design method includes a series of personal approach measures resulting in better response rates.[8,10,27,44] Hence, additional contacts in postal or in-person surveys by themselves do not enhance response rates. However, mailings as part of a personalization process could be beneficial.[30]

Interestingly, for health care professionals we do see a significant effect of additional contacts on response rates in email and webbased surveys. A systematic review of 69 Internet-based surveys of health care professionals in 48 studies also reported a significant increase in response rates after sending reminder emails.[11] Notably, no additional contact appears to

generate the highest response rate in our comprehensive analysis. This could be due to selection bias where researchers achieving a high response rate are less inclined to send follow-up emails. There is also a heterogeneity in this group because of likely nonreporting of reminder emails, so there might be a (stronger) beneficial effect on response rates from reminder emails for online or email questionnaires which we cannot identify. In our series, follow-up negatively impacts response rate in "in person" patient surveys. This is possibly an effect of the very small sample size and thereby more pronounced survey-specific factors.

Although guidelines exist, survey study methodology is often still questionable or at least not reported. The American Association for Public Opinion Research (AAPOR) has published a code of ethics and minimum disclosures for researchers.[45] A separate checklist for internet surveys (CHERRIES) was presented by the Journal of Medical Internet Research.[46] The "Strengthening the Reporting of observational studies" (STROBE) statement does offer checklists for epidemiological cross-sectional studies, but these do not offer reporting characteristics unique to surveys.[47] There is considerate literature in the social sciences on study design and reporting, but a considerate amount of surveying attempts do not adhere to these guidelines.[48] For example, even response rate itself is reported ambiguously. Does one include all the returned questionnaires or only the completed ones? A 2011 review showed that 154 of 165 journals do not provide guidance on survey reporting, whereas 82% have published survey research.[49] These results show that, although separate guidelines exist, there is little control on survey reporting and the need for a well-developed widely adopted reporting guideline is there.

Our analysis presents a unique global overview of reported response rates in surgical survey studies and shows what response rates depend on and are influenced by. In-person surveying has the best results, but is time-consuming and relatively expensive. Postal surveying delivers consistent response rates but is more rigid, depends on accurate mailing lists, offers less certainty about who completed the survey, and is more susceptible to literacy bias.[50,51] Ubiquitous digital connectivity promises fast, low-cost, real-time monitored surveying but is seriously threatened by low response rates and often flawed survey design.

In the era of high patient awareness and increasing demand from government and insurance carriers, the need for quality control has pushed the limits of survey attempts and will continue to do so. Expert consultation should be sought before attempting a survey. Well-defined questions, survey composition, and sample selection can add much needed value to conclusions drawn from survey studies. The variance in reported response rates, signifying the heterogeneity in survey response, shows that it is imperative to reach each interviewee personally and in the right manner. Mixed-mode designs (ie, an email followed by a telephone call) tailored to the targeted population (ie, student vs old age pensioner) will improve response rates significantly.[23,44,52–54] Finally, a clear study design and description will help compare survey attempts and identify key influencing factors on survey outcome. This study has a few shortcomings that need to be addressed. Our search algorithm revealed a

vast amount of studies, although we realize that surveys could have been missed. Second, choosing to reply to a survey is rather personal and depends on several variables. Many aspects of survey design that influence response rates are difficult to reproduce such as wording, length and number of questions, and personalization of a cover letter.[6,8–10] Salience is one of the key factors to influence response rates.[55–62] No review can account for these factors, and to maximize response rates future studies should consider that. We identified those aspects of survey design that can be monitored and reproduced. Finally, surveys often lack a properly defined methodology, which hinders objective comparison of outcomes. The type of questionnaire or follow-up is not always mentioned. Our analysis is limited by its data, which is heterogeneous at best. Uniform reporting of outcomes will help improve the predictive value of future survey study analysis.

In conclusion, the quality of a survey depends on how its questions are answered and how often it is replied to. Response rate is measurable and is influenced by many amendable factors. Overall, patients partake more often in surveys then health care professionals regardless of country, survey mode, or follow-up. Follow-up appears to improve response rate in online surveys aimed at health care professionals, whereas effect on patient surveys remains unclear. Personal and postal surveys do not seem to benefit from follow-up. Our global review provides a first overview of surgical survey response rate and can be used as a quality reference in peer review. This review will aid researchers in future survey study design; it is up to the surveyor to choose depending on their specific goals and resources.

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CHAPTER 8

Survey response in colorectal surgery. A systematic review

Vincent M. Meyer, Stan Benjamens, Joost Keupers, Louise B.D. Banning, Robert A. Pol, Johan F.M. Lange

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ABSTRACT

Background
Survey research is widely used for developing value-based management strategies in colorectal surgery. However, declining response rates threaten the validity of results. Our aim is to identify factors that influence response rate in colorectal surgical surveys and provide recommendations for future survey design.

Methods
We performed a (MEDLINE) search between 2007 and 2020 for survey studies in colorectal surgery providing response rates.

Results
Our search revealed 5693 studies, of which 128 studies were included. Patients with colorectal cancer have a lower mean response rate than patients with benign pathology (62.8% vs 75.5%, $p < 0.001$). Response rate depends on the mode of survey; conducted in person (76%), postal (68%), email (61%) and web-based (44%). Patients participate more often than doctors ($P < 0.001$). Reminders can positively influence response rates in postal patient surveys ($p = 0.03$). The proportion of web-based doctor surveys has grown over time ($p < 0.01$) and overall survey response is declining over time ($p = < 0.01$).

Conclusion
In-person surveying should be explored first in colorectal surgery, especially when addressing colorectal cancer patients and doctors. Reminders are useful to boost response rate in postal surveys directed at patients. Web-based doctor surveys generate the lowest response rate. As response rate is declining, it is important to address these factors when designing and reviewing colorectal surgical survey studies.

Keywords
Survey, Colorectal surgery, Response rate, Colorectal cancer, Postal

INTRODUCTION

Expert opinion of medical specialists and patient-reported outcome are essential for everyday surgical decision making. The all-important patient perspective or outcome is often derived from surveys. Survey research has optimalized the monitoring of patient's quality of life and functional outcome after colorectal surgery as well as evaluating common practice among colorectal surgeons.[2–5] Currently, survey reported outcomes have become essential in regulatory decision making in clinical medicine.[6]

The increased interest in surveys has changed the surveying landscape with the mandate of more and more reliable outcomes. However, the surge in the number of surveys has decreased the general willingness to participate in a survey.[7–9] Unfortunately, this is reflected by a trend of declining response rates over time.[9–12] A low response rate may lead to a selection bias which may weaken the validity of results and is regarded as a limitation by peer reviewers.[13]

There is some evidence that response rates are influenced by the patient's disease, however this evidence is limited. In colorectal surgery there are specific challenges to address. Patients with colorectal cancer for example, may participate less often than breast or prostate cancer patients.[14,15] In addition, a previous study has shown that response rate in colorectal patients is also determined by the survey mode.[16] Finally, surveys in gastro-intestinal surgery nowadays often compromise on methodology and design.[17]

Despite efforts to produce helpful guidelines in the literature, elementary methodological mistakes such as inadequate patient inclusion and choice of (mixed) survey mode are still common leading to low response rates and questionable outcomes.[18,19] It is therefore our hypothesis that patient's disease, survey mode, reminders and type of interviewee can influence survey response.

Hence, we performed a systematic review of response rates to surveys conducted in the field of colorectal surgery. We present different factors concerning survey administration that affect response rate and provide recommendations for colorectal surgery survey design.

MATERIALS & METHODS

Study selection

Colorectal survey studies were identified from a surgical survey database [20]. For this database, the National Library of Medicine (MEDLINE/ PubMed) was systematically searched from January 1, 2007 to February 1, 2020 as follows: (((questionnaire) OR survey) AND "response rate") AND (surgery OR surgical). The review process was discussed in detail with all authors beforehand. Studies were independently screened by 2 authors (V.M. and S.B.). Studies were marked if one of the authors doubted suitability and subsequently checked by the first author to ensure uniform reporting. In case of disagreement, consensus was reached through discussion with all authors. Studies reporting response rates to colorectal surgery questionnaires conducted in the English language were included. When studies reported response rates of multiple types of interviewees or modes of survey, these sub results were included separately. Studies reporting multiple surveys over time were excluded due to possible bias. Reviews, conference abstracts, case reports and studies reporting from other

fields of surgery or medicine, paramedicine or nursing were also excluded. PubMed was checked for cross-references for every included article. This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements checklist including the publication of a PRISMA flow diagram (online supplement 1).[21]

Data analysis

Surveys were categorized according to disease and benign or malignant nature. The category 'complications' contains surveys regarding surgical site infections, anastomotic strictures, enterocutaneous fistulae and social and psychological adverse outcomes of colorectal surgery. Survey mode was categorized into conducted in person (face-to-face or telephone), postal, email, web-based (in case of an online questionnaire) and a miscellaneous group, with mixed-mode or undefined mode of survey. Emails with a link to an online survey were categorized as webbased. The number of follow-up contacts were classified as 0, 1 and 2 or more. The response rate per country was described for all countries with ≥ 5 identified surveys, otherwise surveys were described as part of a continent or as miscellaneous for collaborations between continents. The response rate per scientific journal was described for the 7 journals with the highest number (≥ 5) of identified survey studies. Impact factor was derived from the Journal Citation report 2020.[22]The data are presented as mean (standard deviation, (SD)). Categorical and dichotomous outcomes were expressed as frequencies and percentages. Statistical analysis of these outcomes and their intergroup variation was performed by using the Pearson's chi-square test and Fisher's exact test. In case of ranked variables (i.e. year cohort) a linear-by-linear association was used. Student's t-test was performed to compare between two normally distributed variables. ANOVA was used to assess for a possible correlation between response rate and >2 level variables, such as mode of survey. A p value < 0.05 was considered statistically significant. If assumption of normality was violated, Kruskal-Wallis test was used. In case of an ordinal independent variable (i.e. year cohort or impact factor) Jonckheere-Terpstra test was used. Statistical analyses were performed with IBM SPSS version 23.

RESULTS

Overall, 128 studies from our initial search of 5693 records met the inclusion criteria (Supplement 1). Fifty-two (69.6%) patient surveys were conducted by post, 15 (20.0%) used a mixed-mode design, 4 (5.3%) were conducted in person and 2 (2.7%) were conducted via a web-based application and 2 (2.7%) by email. Twenty-four (45.3%) doctor surveys were conducted via a web-based application, 20 (37.7%) by post, 4 used either mail (7.5%) or a mixed-mode design (7.5%) and 1 was conducted (1.9%) in person. Type of disease and anatomical location Figure 1 shows the distribution of surveys and mean response rate per disease category. Overall, there was no significant difference in mean response rate between diseases (p = 0.09) in 100 studies. In 97 out of 128 studies, a differentiation could be made between benign and malignant pathology. The mean response rate in patients was 75.5(12.3)% for benign pathology and 62.8(16.0)% for malignant pathology (p = 0.001). This effect remained

significant after correction for survey mode (p = 0.001). For doctor surveys, mean response rate in benign pathology was 54.1(26.6)% and 49.4(23.3)% in malignant pathology (p = 0.63). In 38 studies regarding benign disease, no statistically significant difference in response rate between diseases was seen (p = 0.56). In 53 out of 128 studies, a stratification by either colon, rectum or (peri)anal pathology could be made. No statistically significant effect of localization of disease on response rate was seen (p = 0.36).

Survey mode & interviewee type

Response rate depended on the survey mode (p < 0.01). Surveys conducted in person yielded a mean response rate of 76.4(±10.2)%, followed by postal 68.0(±17.1)%, email 61.2(±26.0)% and web-based studies 44.2(±22.1)%. Response rate was also dependent on interviewee type. The mean response rate was 69.6(±16.0)% for patient surveys and 52.9(±22.7)% for doctor surveys (p < 0.001). The correlation between interviewee type and response rate remains when corrected for survey mode (p < 0.001). Web-based patient surveys yielded a 56% response rate in two studies, patient postal surveys had a mean 65% response rate in 26 studies and in person studies directed at patients reached an 84% response rate. Figure 2 shows the mean response rate per survey mode and for patients versus doctors.

Follow-up contact

Response rate was not affected by follow-up contact, except in cases of postal surveys of patients (p = 0.03). A single postal patient survey had a mean response rate of 65.8 (17.4)%. A postal survey followed by a reminder yielded a mean response rate of 75.3(11.6)%. Two and three or more reminders led to a mean response rate of 83.6(6.1)% and 66.0(9.3)%, respectively.

Changes over time

Over time there has been a change in preference for survey type. Figure 3 shows the percentage share of individual survey modes per time cohort of 3 years. An increase in survey studies and a significant proportional increase in web-based surveys was observed over time (p = 0.01). However, a decrease in mean response rate over time cohorts was observed (Figure 3, p = 0.003).

Journal response rate

The 128 included studies were published in 63 scientific journals. Figure 4 provides an overview of the journals with ≥5 survey publications and their mean response rate. Mean response rate and impact factor (IF) varied between the International Journal of Colorectal disease with IF 2.10 and 7 studies (76.4(13.3)%), British Journal of Surgery with IF 5.67 and 5 studies (74.5(12.8)%), Diseases of Colon and Rectum with IF 3.99 and 19 studies (66.9(19.6)%), Colorectal Disease with IF 2.77 and 17 studies (66.8(17.6)%), World Journal of Surgery with IF 2.23 and 5 studies (64.5(33.2)%), Techniques in Coloproctology with IF 2.72 and 6 studies(52.4(27.2)%) and the Journal of Surgical Research with IF 1.84 and 5 studies(44.6(14.0)%). Despite the wide range in response rate between the journals, there is no significant effect of impact factor on response rate (p = 0.41).

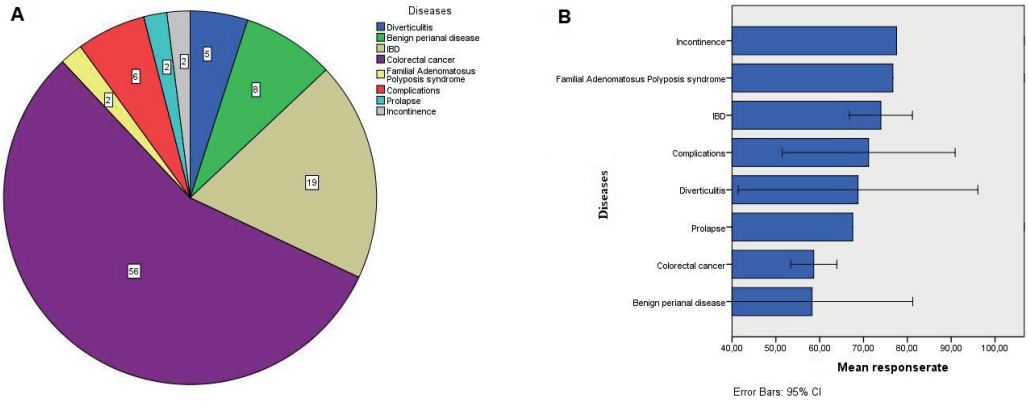

Figure 1 | (A) shows number of survey studies per disease category. *(B) shows mean response rate per disease category. CI bars for categories >3 studies.*

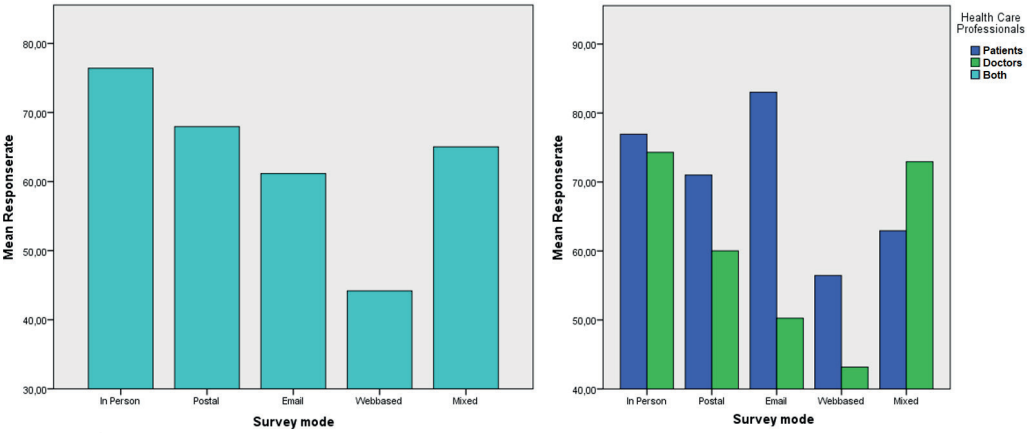

Figure 2 | Left hand side shows mean response rate per mode of survey (p < 0,01).
Right hand side shows mean response rate for patient (p = 0.16) and doctor surveys (p = 0.03) per mode of survey. P-value for ANOVA. Only two email studies were directed at patients.

Geographic distribution

The 128 included studies originated from 18 countries or geographic areas. Figure 5 shows the distribution of mean response rate for the top ten published countries (≥5 studies). Sweden with 7 studies (83.3(8.1)%) and the Netherlands with 15 studies (76.6(13.4)%) show the highest mean response rate, while the USA with 35 studies (53.5(21.5)%) and Australasia with 14 studies (54.8(18.4)%) have a much lower score. In Sweden (86%) and the Netherlands (80%) almost all surveys were conducted via post in contrast to the USA (41%) and Australasia (36%).

DISCUSSION

Our study shows that the response rate in surveys conducted in colorectal surgery patients, depends on the type of disease. Response rate further depends on a combination of interviewee type, survey mode and reminders. Overall survey response is declining over time and therefore all these factors should be addressed in survey design. Surveys conducted in patients with a malignancy had a lower response rate (62.8%) than those conducted in patients with benign disease (75.5%) ($p = 0{,}002$). Both groups differ in several aspects. Benign disease consisted mainly of IBD, diverticulitis and peri-anal disease whereas malignancy addressed solely colorectal cancer patients. In previous studies, a lower response rate has been linked to a worse self-reported health and mortality rate which is associated with cancer patients.[23–27] This finding is again confirmed in our study. In a cohort of 1200 patients of the Pennsylvania Cancer Registry, colon cancer patients specifically responded less often (55% response rate) than breast and prostate cancer patients. This effect remained after controlling for sex, age, marital status and cancer stage ($p < 0{,}001$).[14] A different study showed that colon cancer patients had a lower response rate (30% response rate) than breast cancer patients .[15] This has been called the 'healthy volunteer effect', where healthier candidates are more likely to participate in a survey.[26,28] This could also explain why colon cancer patients with local disease reply more often than those with metastasized cancer.[14] Thus, one should be aware that poor response rate is more prevalent in this group of patients. In our study, web-based colorectal cancer patient surveys were rare and yielded a mean 56% response rate in two studies. On the contrary, postal survey studies in this group had a mean 65 % response rate in 26 studies and the mean response rate for surveys conducted in person was 84%. A previous study confirmed that postal surveys with follow-up contact will reach higher response rates than web-based alternatives in colorectal cancer patients.[16] Thus although a lower response rate can be expected in colorectal cancer patients, this effect can be minimized with the appropriate choice of survey mode.

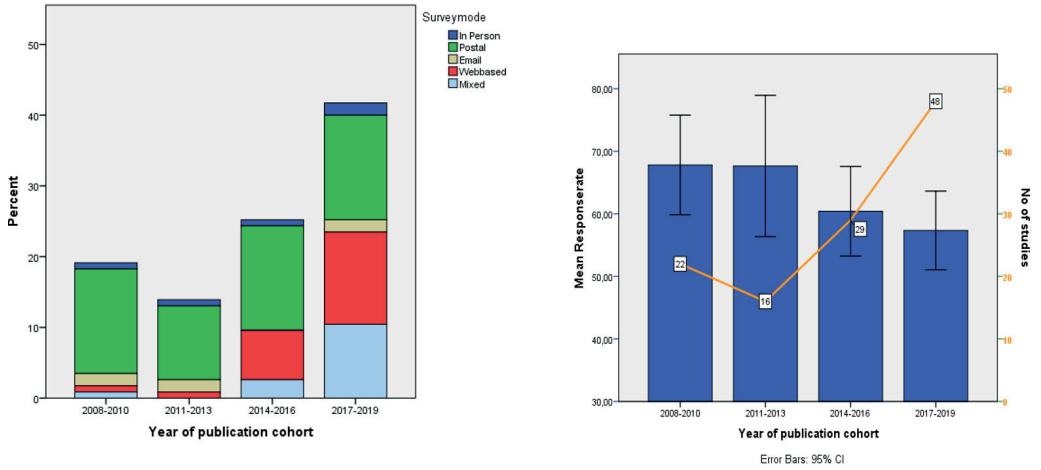

Figure 3 | Left hand side shows percentage share of individual survey modes per 3-year time cohort. *P-value for Pearson's chi-Square test. Right hand side shows mean response rate over time (p = 0.003) and number of studies. P-value for Jonckheere-Terpstra test.*

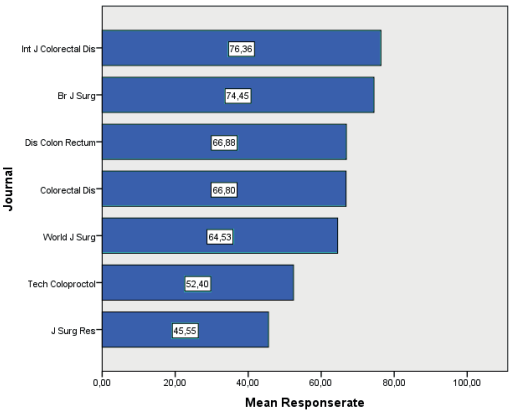

Figure 4 | The mean response rate in 7 most published journals.

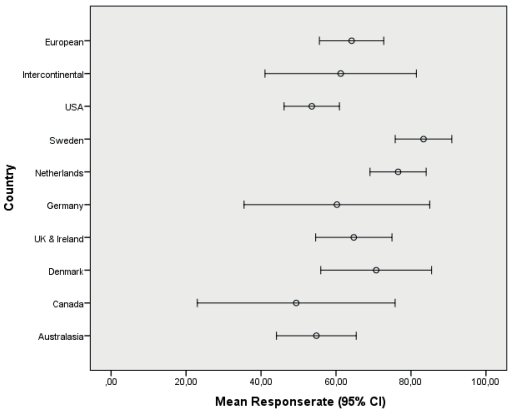

Figure 5 | Mean response rate (95% CI) per country or geographic area.

Surveys conducted in person achieved a mean response rate of 76.4%, followed by postal 68.0%, email 61.2% and web-based surveys 44.2%. These findings correspond well with survey literature.[29–33] It is therefore imperative to explore the possibility of interviewing in person before a postal or web-based version. Allocating more resources this way (if available) allows for a higher response rate and therefore better interpretation of survey results. Internet surveys (and conclusions drawn from them) generally perform worse and should always be treated with care as methodological errors are common.[34–37] Expert consultation should be sought to address the common pitfalls in online surveying specifically.

Reminders are the most obvious tool to produce a higher response rate. In our subset of patient surveys, a positive effect of subsequent reminders was observed in postal surveys. Surveys with three reminders or more did not increase response rate; this likely illustrates that multiple reminders will not overcome shortcomings in survey design. In general, a more intensive follow up to postal surveys appears to improve response rate although a "cut-off" has not been identified.[38] A 2008 Cochrane review analyzed 481 postal trials and concluded that follow-up contact was significantly associated with a better response rate (OR 1.35; 95% CI 1.18 to 1.55; $p < 0.01$).[39]

In our study, reminders in web-based surveys did not affect response rate. The Cochrane review analyzed 32 electronic trials and also found no advantage in using reminder emails.[39] Thus, although frequently used, reminders are not always effective. Reminders in postal survey studies could improve results in the colorectal patient population, but seem to have no effect in web-based surveys and when addressing the colorectal surgeon in general.

Thus, a well-designed survey should also consider the interviewee. Our analysis showed a mean response rate of 69.6% for 75 patient-orientated surveys and 52.9% for 53 surveys among doctors ($p < 0.01$). Although doctors receive the most web-based surveys which negatively affects response rate, the association between interviewee type and response rate remains when corrected for survey mode ($p < 0,01$) [29,30]. Doctor surveys do generate a lower response rate, the main reasons being lack of time or salience. Short on time, doctors will not complete a survey if the value of the study is considered too low.[12,40] Concerns on confidentiality and perceived biased questioning also plays a role.[41] Therefore, doctor surveys should specifically be designed to maximize salience and minimize effort.[42,43] Previous studies suggest a reasoned and strict selection of participants and survey mode, personalization, providing an incentive, shortening a survey, using closed questions and pre-stamping a return envelope.[12,30,44–47]

We found geographical variations in survey response rate over 18 countries or geographic areas, varying from 83.3% in Sweden to 53.5 % in the USA. This represents at least partially an effect of survey mode, where in the high response rate countries (Sweden and the Netherlands) the majority of surveys were sent by post in comparison to a preference for a web-based design in the low response rate countries/regions (USA and Australasia).

Finally, response rate is often critiqued in peer review and considered a surrogate of quality or impact. However, a review in 2011 showed that 154 out of 165 journals do not offer guidelines for survey reporting, although 82% have published survey research.[48] In our analysis, we found no relation between mean response rate per journal and impact factor.

Implications

Survey response depends on a large variety of factors and is therefore highly variable in the literature. However, we can identify those factors that influence survey response in colorectal surgery to give context to each unique survey's reported response rate.

Our study shows that the option of in person surveying should be explored first. Postal and web-based surveys respectively will require less resources, but achieve a lower response rate. This is especially important in the colorectal cancer population, where overall response rate is shown to be significantly lower compared to benign disease but can be in part counteracted by appropriate choice of survey mode. Doctor surveys yield lower response rates then patient surveys and previous research has shown that doctor surveys should be short, easy to return, salient and appear reliable.[12,41] As in the colorectal cancer population, appropriate choice of survey mode can influence response rate.

Based on our results, we advise selective use of reminders. Only when choosing a postal survey method in the colorectal patient population, reminders should be a part of survey design. Although considered important in peer review, there is no relation between mean response rate and impact factor. Although many guidelines are available, they are generally not reported. Stricter journal design requirements and adherence to relevant guidelines such as Checklist for Reporting Results of Internet E-Surveys (CHERRIES), the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement, the Enhancing the Quality and Transparency Of health Research (EQUATOR) initiative and the Survey Reporting GuidelinE (SURGE) would help to improve and compare results.[49–52]

Limitations

This study has a few shortcomings to be addressed. First, a substantial part of the response rate is associated with measurable aspects such as interviewee characteristics, mode of survey and follow up but other more personal factors cannott be reproduced. This paper focuses on measurable, amenable and known survey characteristics, but more patient centered data such as outcome of treatment, length of admission and complications which could not be derived from these studies could influence patient response. Secondly, there is a large heterogeneity in (non)reporting of response rate (complete vs incomplete questionnaires), recruitment, incentives, use of cover letter, (validated) questionnaire, actual survey mode and follow up. This was exemplified by the relatively large proportion of 'mixed-mode' studies. Also important, survey characteristics such as wording, length, answer options and other possible relevant variables could generally not be extracted from the included studies. For these reasons, a prediction model could not be construed. Further studies will benefit from guideline adherence in survey design and concomitant uniform reporting of outcomes so that conclusions drawn from surveys can be compared, better controlled and in the future, predicted.

CONCLUSION

In-person surveying should be explored first in colorectal surgery, especially when addressing colorectal cancer patients and doctors. Reminders are useful to boost response rate in postal surveys directed at patients. Web-based doctor surveys generate the lowest response rate. As response rate is declining, it is important to address these factors when designing and reviewing colorectal surgical survey studies.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.sipas.2022.100068.

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CHAPTER 9

Surveys in Surgical Education: A Systematic Review and Reporting Guideline

Louise B.D. Banning, **Vincent M. Meyer**, Joost Keupers, Johan F.M. Lange, Robert A. Pol, Stan Benjamens

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ABSTRACT

Objectives

Survey studies are a commonly used method for data collection in surgical education research. Nevertheless, studies investigating survey design and response rates in surgical education research are lacking. The aim of this study was to gain an insight into survey response rates among surgical residents and medical students, and provide an initial reporting guideline for future survey studies in this field.

Design

PubMed (MEDLINE) was systematically searched for survey studies in surgical education from January 2007 until February 2020, according to the PRISMA statements checklist. Study selection was conducted by 2 authors, independently. Surveys directed at surgical residents and/or medical students were included if data on response rates was available. Studies reporting solely from nonsurgical fields of medicine, paramedicine, or nursing were excluded. Subgroup analyses were performed, comparing response rates for varying modes of survey, per country, and for the 10 journals with the most identified surveys.

Result

From the 5,693 records screened for a larger surgical survey database, a total of 312 surveys were included; 173 studies focused on surgical residents and 139 on medical students. The mean (SD) response rate was 55.7% (24.7%) for surgical residents and 69.0% (20.8%) for medical students. The number of published surveys increased yearly, mostly driven by an increase in surgical resident surveys. Although most surveys were Web-based (n = 166, 53.2%), this survey mode resulted in the lowest response rates (mean 52.6%). The highest response rates, with a mean of 79.8% (13.1%), were seen in in-person surveys (n = 89, 28.5%). Wide variations in response rates were seen between different countries and journals.

Conclusions Web-based surveys are gaining popularity for medical research in general and for surgical education specifically; however, this mode results in lower response rates than those of in-person surveys. The response rate of in-person surveys is especially high when focusing on medical students. To improve reporting of survey studies, we present the first step towards a reporting guideline.

Keywords

Surveys and questionnaires, Systematic review, Education, General surgery

INTRODUCTION

Survey studies are frequently applied for the evaluation of research into education for surgical residents and medical students.[1] These surveys form a key element for improving medical education and assessing the performance, attitudes, and well-being of the residents and students.

Surveys can be conducted in modes such as in-person interviews, postal questionnaires, and Web-based surveys,[2] the last of which has gained popularity in recent years.[3] It has been well established that different survey types will produce a variable response rate, which, in turn, affects their reliability and interpretation. A low response rate introduces a nonresponse bias and wider confidence intervals, thereby affecting the quality of conclusions drawn from a survey.[4] In-person surveys show higher response rates than studies with a postal and/or Webbased design but are more expensive to perform. Webbased surveys, on the other hand, are easy to implement and more suitable for a large sample size, but response rates are relatively low.[5,6] Specific to medical students, researchers found a 50% drop in the response rate when a postal survey was replaced by an e-mail-based survey.[7]

Although medical students are frequently approached for surveys, little is known about their rate of participation[8–10] Medical students and residents are subject to the hierarchy at medical school and can react and respond to survey requests differently from other health care professionals.[11] It is thus difficult to compare their participation rates. A study that analyzes the rate of participation by this specific group in different survey types is needed to maintain reliable survey results. However, studies investigating the survey methods and response rates in surgical education research are currently lacking.[12] Analyzing the participation in surveys and the survey methods in specific populations, e.g., medical students and residents, can provide essential information to improve the quality of future surveys and survey research in general.[5]

Survey research is often hindered by unclear and inconsistent reporting of the methods used, e.g., the response rates and the number of survey requests.[10,13] This lack of information about survey methodology hampers the reliability and reproducibility of the results. Therefore, the implementation of a standardized reporting guideline for surveys in surgical education is needed. The aim of our study was to perform a systematic review on surveys in surgical education, with an emphasis on response rates for varying modes of survey, and to present an initial reporting guideline for future studies.

METHODS

PubMed (MEDLINE) was systematically searched from 1 January 2007 to 1 February 2020, resulting in the surgical survey database referred to by Meyer et al.[2] in the Annals of Surgery. For this database, the following MeSH term or keywords were used: ("questionnaire" or "survey") and "response rate" and ("surgery" or "surgical"). A subgroup of surgical resident and medical student surveys was selected by searching for "resident," "trainee," "student," or "intern". Studies were included if matching criteria for surgical resident or medical student and data on response rates were available. Reviews, conference abstracts, case reports, and studies reporting solely from nonsurgical fields of medicine, paramedicine, or nursing, were

excluded. Studies reporting the use of various survey types were also excluded. Two authors (L.B.D. and S.B.) independently carried out the study selection based on the stated criteria. This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statements checklist, including the publication of a PRISMA flow diagram.

Surveys were stratified as: (1) in-person (face to face or telephone), (2) postal, (3) e-mail, (4) Web-based with an online questionnaire, and (5) a miscellaneous group with mixed-mode surveys. The number of survey requests sent to the subjects was classified as a single request or multiple requests. The response rate per country of origin was described for all countries with ≥3 identified surveys; otherwise, surveys were described as part of a continent or as miscellaneous for collaborations between continents. The response rate per scientific journal was described for the 10 journals with the highest number of identified surveys, displaying journals with ≥5 identified surveys.

To establish an initial reporting guideline for surveys in surgical education, reporting guidelines available in the literature were collected. The EQUATOR (Enhancing the QUAlity and Transparency Of health Research) network was used to select the SURGE and CHERRIES guidelines as the most appropriate reference guidelines.[14] The initial guideline was written in accordance with the points raised in the reports on good practices in survey research.[5,15–22] The reporting guideline by Moher et al.[22] was used an example.

The data are presented as mean (SD). Groups were compared by Student t test for differences between 2 groups, and one-way analysis of variance for differences between the 5 survey modes. $p < 0.05$ was considered statistically significant. Statistical analyses were performed with R: A Language and Environment for Statistical Computing v1.0.153 for Mac (R Foundation for Statistical Computing, Vienna, Austria), using the software R Package "ggplot2."

RESULTS

In total, 5,693 records were retrieved from the systematic literature search, with 312 surveys meeting the selection criteria. A detailed description of the inclusion and exclusion of records is provided as a PRISMA flow diagram (online suppl. Figure 1; for all online suppl. material, see www.karger.com/doi/10.1159/000516125). Of the identified surveys, 173 focused on surgical residents and 139 on medical students. One hundred and sixty-six (53.2%) surveys were classified as Web-based, 89 (28.5%) as in-person, 41 (13.1%) as e-mail, and 16 (5.1%) as postal mode. The majority of surveys was performed in the USA (n = 163, 52.2%), followed by Canada (n = 32, 10.2%), and the UK (n = 26, 8.3%).

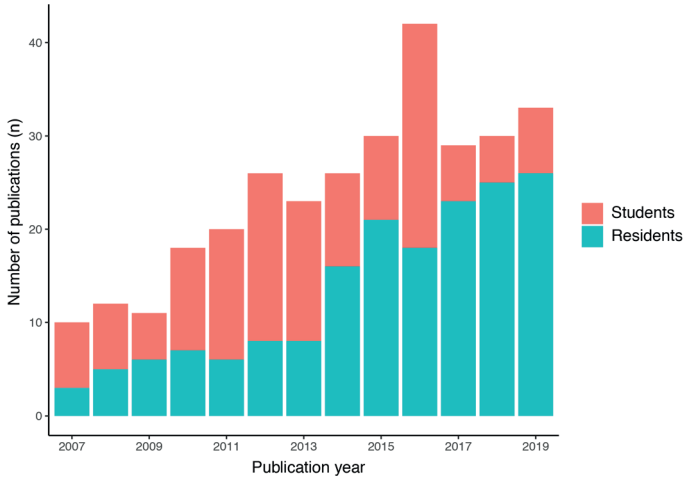

Figure 1 | Number of publications identified for each year, stratified for surgical residents and medical students, from 2007 to 2019.

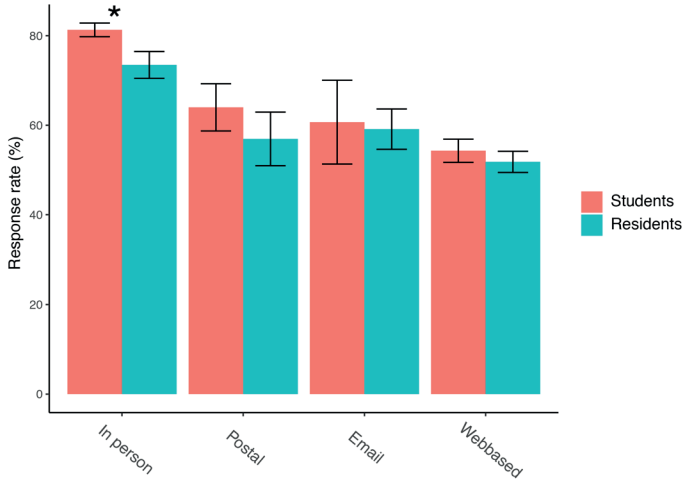

Figure 2 | Mean (SD) response rate for different modes of survey, stratified for surgical residents and medical students. *p value for Student t test, with * p = 0.028 indicating significance.*

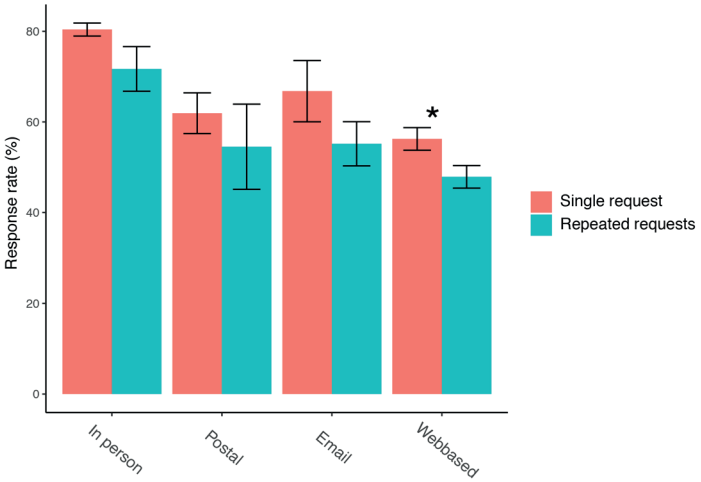

Figure 3 | Mean (SD) response rate for different modes of survey, stratified for single request and repeated requests surveys. *p value for Student t test, with * p = 0.028 indicating significance.*

Response Rates for Surgical Residents and Medical Students

The annual number of published surveys in surgical education increased from 10 in 2007 (3 surgical resident and 7 medical student surveys) to 33 in 2019 (26 and 7, respectively) (Figure 1). The mean (SD) response rate for all 312 surveys was 61.6% (23.9%), with a mean of 55.7% (24.7%) for surgical residents and 69.0% (20.8%) for medical students ($p < 0.0001$). When comparing the response rate between surgical residents and medical students for different modes of survey, the mean response rate was only statistically different for in-person surveys, with a mean of 73.5% (12.4%) and 81.3% (13.0%), respectively ($p = 0.028$; Figure 2).

Response Variation for Modes of Survey and Repeated Requests

A significant difference in response rates was observed between different survey modes ($p < 0.0001$), with in-person surveys resulting in the highest response rate (mean 79.8% (13.1%)) and Web-based surveys in the lowest (mean 52.6% (23.2%)). The mean response rate was 59.4% (25.7%) for e-mail surveys and 59.1% (17.7%) for postal surveys. Lower response rates were observed for studies reporting multiple/repeated survey requests than those reporting a single request, with a mean of 51.3% (22.3%) and 67.2% (22.9%), respectively ($p < 0.0001$). When comparing the difference between multiple and single requests for different modes of survey, the mean response rate was only statistically different for Web-based surveys, with a mean of 47.9% (21.2%) and 56.2% (24.2%), respectively ($p = 0.019$; Figure 3).

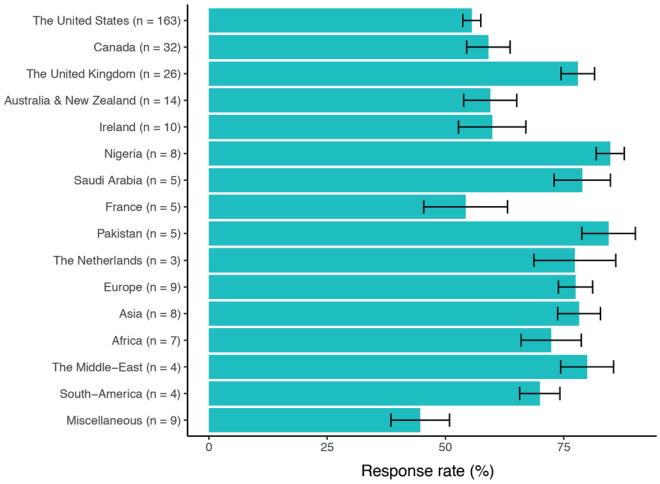

Figure 4 | Mean (SD) response rate per country or continent of origin.

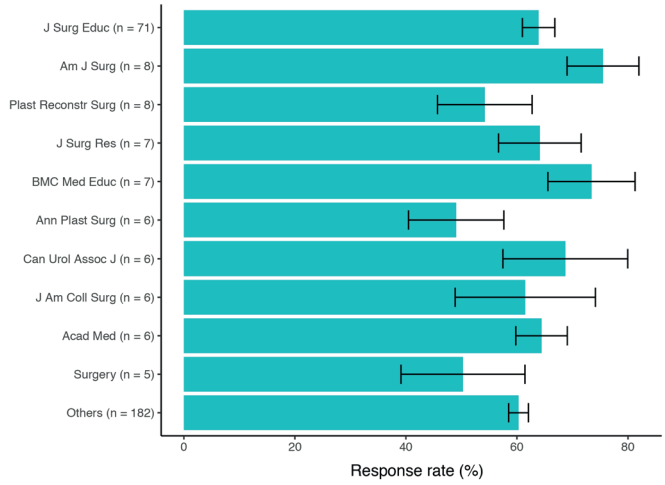

Figure 5 | Mean (SD) response rate for the 10 journals with the highest number of identified surveys.

Table 1 | Checklist of items to include when reporting a survey.

Section	Topic	Checklist item
Title		
	Title structure	1. Identify the study as a survey and address the subjects of the survey
Abstract		
	Concise methodology	2. The subject group, mode of survey, study period, number of subjects approached, and number of requests sent
	Structured results	3. The total response rate and number of subjects included
Introduction		
	Rationale	4. Clear description of the rationale, referring to important previous studies
	Objectives	5. Concise study aim, including the subject group and main research question
Methods		
	Subject group	6. The specific subject group, including eligibility criteria
	Mode of survey	7. Mode of survey, such as in-person, postal, e-mail, or Web-based
	Survey strategy	8. The predefined plan for the number of subjects to be approached (justification of sample size), the number of requests to be sent, and who will send the requests
	Ethics	9. Institutional review board (IRB) approval, study funding, and informed consent
	Survey items	10. A summary of the survey items, with information on reliability and validation, and the full survey text as supplementary information
	Missing data	11. A description of missing data for each survey item
	Data analysis	12. Analyses of qualitative and quantitative survey data, including the applied methods for statistics
Results		
	General survey results	13. Number of subjects included, the total response rate, and response rate for each request sent
	(Non)respondents	14. Subject characteristics of respondents and nonrespondents
Discussion		
	Reflection	15. Critical reflection about the results and the available literature
	Limitations	16. Potential bias caused by survey methodology, subject selection, and nonrespondents
	Conclusions	17. Interpretation of the results, in line with the study aim

Response Variation for Countries and Journals

A wide variation in response rates was seen worldwide, with a mean response rate of 55.6 (24.3%) in the USA, 59.0% (26.0%) in Canada, and 78.0% (18.1%) in the UK. The highest mean response rate of 84.8% (8.4%) was seen in Nigeria and the lowest response rate in France with 54.3% (19.8%) (Table 1. Checklist of items to include when reporting a survey 4). In Nigeria, all the surveys were in-person surveys; in France, all the surveys were Web-based (online suppl. Table 1. Checklist of items to include when reporting a survey 2). A variation was seen across the 10 journals with the highest number of identified surveys, with a mean response rate of 63.9% (24.6%) for the Journal of Surgical Education, 75.5% (18.3%) for the American Journal of Surgery, and 64.1% (19.7%) for the Journal of Surgical Research. The highest mean response rate was seen in the American Journal of Surgery and the lowest in the Annals of Plastic Surgery, with 49.1% (21.0%) (Figure 5).

Initial Reporting Guideline

With 17 items that covered the key elements of a survey study manuscript, a clear and consistent presentation of the methodology and outcomes was generated (Table 1). The most important items of this guideline are the eligibility criteria for the selection of subjects, the mode of survey used, the survey items included, the number of subjects included, and the total response rate.

DISCUSSION

The yearly number of published surveys in surgical education has increased in the past 13 years, especially in surveys focusing on surgical residents. In-person surveys resulted in the highest response rate and Web-based surveys in the lowest response rate. Surgical residents responded less often to survey requests than medical students did, especially when the surveys were performed in person.

Previous studies evaluating response rates among different health care professionals showed a variety of outcomes. A review evaluating the response rate in doctors found that they have a lower response rate than patients (mean: 53.3 and 70.0%, respectively[2]). Response rates in studies on surgeons, for example, are often very low (15%), which could be explained by their busy workload and limited priority for participation.[23] Although medical students and residents are part of the health care system in terms of pursuing a medical career, their behavior in terms of survey participation cannot be compared to the behavior of doctors.

Our results are in agreement with a study on health profession residents, mostly medical students, that found a response rate of 71.3% (69.4% for medical students).[12] The relatively high response rate in surgical residents and medical students could be explained by the hierarchy they are subjected to in the health system, leading to a higher priority to participate.[11] We found a higher response rate for medical students than surgical residents, possibly explained by the combination of a higher rank in the hierarchy for residents and a busier work-schedule.

In our study, we found that in-person surveys resulted in the highest (79.8%) and Web-based surveys in the lowest (52.6%) response rate. These results are in line with previous studies .[3,16,24,25] However, because of the low response rates, such surveys can be subject to bias because of the self-selection of participants, the so-called "volunteer effect".[26] To increase the response rate, Web-based surveys often use multiple requests for participation. We found that studies using repeated survey requests had lower response rates than those using a single request. This outcome is the opposite of previous studies, suggesting that multiple requests lead to higher response rates.[9,27] According to the current guidelines, certain well-designed surveys achieve a high response rate on initial presentation.[16] When faced with a low response rate, authors are inclined to send additional requests. However, the factors that result in a low response rate in the first round will not be addressed only by sending repeat requests. This may explain why studies with repeated survey requests had a lower overall response rate. It is important to implement strategies to improve the response rate, and therefore decrease the risk of a nonresponse bias. This could be by implementing incentive-based interventions (that use money and design-based approaches), i.e., in-person surveys and user-friendly questionnaires that are not too long.[28,29]

A global variation in response rates was found. Surveys performed in Pakistan had the highest response rate (84.8%) and those in France had the lowest (54.3%). The response rate in the USA was also low (55.6%). These differences can mostly explained by the differences in modes of survey (online suppl. Figure 2). In nonwestern countries, like Nigeria, in-person or telephone surveys are preferred due to limited logistics and internet access.[24] The surveys in Pakistan and Nigeria, the countries with the highest response rate, were all conducted in person, the survey mode proven to lead to the highest response rate.

On the other hand, in France and the USA (the countries with the lowest response rates), the Web-based survey, i.e., the mode with the lowest response rate, was most often used. Another possible explanation could be cultural cross-country differences, like differences in individualism and collectivism.[30,31] However, the literature on cultural difference and survey outcomes is scarce, thus limiting conclusions on this matter.

Strategies to improve response rates and therefore the quality of surveys are often lacking. A systematic review of 100 Web-based and 100 non-Web-based surveys showed that many items of the Survey Reporting GuidelinE (SURGE) or the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) guideline were not reported.[20] To provide a framework for surveys in surgical education, we compiled a 17-item initial reporting guideline to ensure clear and consistent presentation of the methodology and outcomes of survey studies in this field.

To our knowledge, this is the first systematic review on the response rates of surveys in surgical education. Strengths of this study include the systematic approach following the PRISMA reporting guideline and the relatively large number of survey studies included (n = 312). The main limitation of the study is the quality of the included records, with sparse information available about the methodology of the surveys performed. This limitation hampered a more elaborate analysis of the factors that influence response rates. The reporting guideline for surveys in surgical education can be considered as an initial step towards a broadly recognized guideline, which requires an expert review by means of a Delphi study.[32]

In conclusion, this systematic review on surveys in surgical education demonstrated variations in response rates between different modes of survey, thus highlighting the importance of clear and consistent reporting of survey methodology.

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CHAPTER 10

General discussion and future perspectives

DISCUSSION

PART I Surgical perspective

Patients with a sustained complete clinical response benefit from a Watch & Wait program, as they do not suffer the morbidity of a rectal resection while maintaining an excellent oncological outcome.[1,2] The first reports on organ preservation concerned patients with more advanced tumours where there was an oncological indication for neoadjuvant therapy. The complete response rates were around 15-20% and can be considered as opportunistic or secondary organ preservation. In the last decade there has also been an increasing trend towards planned or primary organ preservation in smaller tumours that do not require neoadjuvant radiotherapy for an oncological indication, but where it can be added with the specific goal to achieve a cCR and omit TME surgery or to perform a local excision of a small remnant. Higher response rates are reported, with organ preservation rates of well above 50%.[3,4] In this strategy the role of radiotherapy is shifting from improving local control and oncological outcome to improving and preserving function and quality of life. However, up to 1/3rd of these patients will still require radical surgery and are thus overtreated, and local excision after RT can significantly affect functional outcome.[5–7] The STAR-TREC trial comparing SCRT vs CRTx with LE if needed is now underway.[8]

Currently, patients are usually restaged after neo-adjuvant therapy after an interval of 6-8 weeks with a DRE, MRI and endoscopy. Standardization of restaging as proposed by Habr-Gama improved the selection for Watch and Wait and allows for a comparison between institutions.[9] Up to 25% of patients will have hidden residual tumour and will present with a regrowth and thus require additional treatment, often radical TME surgery. The current diagnostic methods to detect a complete clinical response are therefore not completely accurate.[10] The endoscopy image is the single most specific modality, with additional biopsy generally not recommended as both falsenegative and false positive findings have been reported.[11] MRI complements the diagnosis of a complete response, but is known to overestimate the presence of small (residual) tumour.[12] Especially in primary organ preservation there is a need for predictive markers for radiosensitivity. Where mutational analysis (RAS/BRAF/MSI) can guide targeted therapy, more elaborate whole genome sequencing could possibly select mutations that predict radiosensitivity. Circulating tumor DNA, miRNA and exosomes are associated with response to neo-adjuvant CRTx in rectal cancer and are able to improve prediction of response when used in conjunction with MRI.[13–15] Also, the gut microbiome is different in patients with a pCR after CRTx compared to non-pCR.[16] None of these markers have proven clinical applicability yet in predicting pCR, but are investigated for their potential use.

Another area for improvement is to optimize neoadjuvant treatment to obtain a better response. The first option is the addition of systemic therapy. Total neo-adjuvant therapy (TNT), combination of (chemo)radiotherapy and chemotherapy, was designed to improve distant failure by targeting micro metastases sooner. There are several (ongoing) trials which recently examined TNT. The phase II multicenter OPRA trial failed to show increased DFS for TNT patients compared to historical controls of conventional CRT-TME-adjuvant chemotherapy. However, as a secondary endpoint, did show improved distant control, pCR and organ preservation rates at 3-years for those eligible for Watch & Wait, favoring consolidation over induction chemotherapy with half of patients avoiding surgery.[17] The Rapido and Prodige-23 trials demonstrated improved DFS (not OS), but also somewhat surprisingly showed doubled pCR rates with addition of pre-operative chemotherapy to (SC)RT.[18,19] GRECCAR-12 is a phase III study examining whether TNT followed by local excision in good responders can improve organ preservation at 1-year. Accrual has been completed and results are expected in 2024.
For now, the most effective treatment regimen has not yet been established: induction vs consolidation, doublet vs triplet, short course RT vs CRTx. Future research will show what form of (total) neo-adjuvant therapy will hold the optimal balance between oncological outcome and patient tolerability. A major concern of surgeons regarding TNT is the effect on the quality of the surgery of added waiting time after RT.[20] In Chapter II we have shown that delayed surgery after CRTx does not increase morbidity but the effect after TNT remains unclear. On the other hand, increased waiting time might also benefit response, which can explain the higher observed pCR rate in consolidation vs induction chemotherapy.[21] The downside of more neo-adjuvant chemotherapy are side effects like oxaliplatin-induced neuropathy, and the harm/benefit balance of additional treatment will be an important factor going forward.

A second option is to give a higher radiotherapy dose by boosting the area of the primary tumour. Higher radiotherapy doses lead to more tumor regression.[22] A radiation boost can be achieved with different techniques. The RECTAL-BOOST trial used External Beam RadioTherapy (EBRT) to deliver a boost of 3x5Gy additional to the standard CRTx regimen, which led to increased tumor regression but not increased pCR or sustained cCR.[23] Likely, in these relatively large tumours a higher dose is necessary to achieve full sterilization of the tumor. The introduction of MR-guided radiotherapy has led to more precise therapy allowing for a higher dose to the tumor while avoiding radiation of other organs.[24] Another option is endoluminal boosting with endorectal brachytherapy or contact RT (CXB), where significantly higher boost doses can be administered safely. The OPERA trial showed primary organ preservation at 3-years of 97% after CXB boost (90Gy/3 fractions) compared to 65% after EBRT boost (9Gy/5fractions) in addition to a standard course of 45Gy of chemoradiation in early rectal cancer <3cm.[25] To establish the role of contact RT in secondary organ preservation the OPAXX trial is randomizing near complete responders after CRTx between repeated assessment with LE only in case of persistent tumor or 90Gy/3 fractions. Although radiotherapy dose escalation can improve local control, it does not control microscopic regional or distant disease and is therefore unlikely to improve overall survival.

There is a third option for the small group of MSI rectal cancers: immunotherapy. Immune checkpoint inhibition has shown to be a game changer in tumors specifically with a high mutation frequency and a high level of antigenicity, such as melanoma. In rectal cancer, immune activity measured by tumor infiltrating lymphocytes has shown to be related to prognosis.[26] Recently, Cercek et al published their series of 12 stage II/III MSI rectal cancer patients treated with neo-adjuvant dostarlimab, an anti-PD-1 monoclonal antibody. This treatment was to be followed by CRT and TME surgery for residual disease. However, all patients showed a complete clinical response after 6 months of treatment, maintained with follow-up of 6-25 months. This illustrates the enormous potential of immunotherapy in MSI patients.[27] Compared to chemotherapy and radiation, immunotherapy is a step towards selectively targeting the cancer, hopefully lowering morbidity and improving oncological results. More studies on both MSI and MSS rectal cancer are investigating the role of neoadjuvant immunotherapy or immunomodulation in obtaining pCR.[28]

The role of a local excision in organ preservation is not well defined. At restaging some patients will present with a good response without fulfilling the criteria of a complete response, and are sometimes labeled as near complete responses. Some surgeons advocate a local excision both as a diagnostic tool as well as a therapeutic tool when there is residual tumour. Another approach is to extend the observation interval to allow further regression as this avoids overtreatment in complete responders. The finding in the landmark paper from the IWWD that 99% of patients with a regrowth were amenable for curative salvage surgery, suggest that it is safe to delay surgery in these patients.[1] In chapter III we show that in a large cohort a selected group of regrowths could be treated with a local excision, and that all local recurrences after the local excision were salvageable with a TME. Of course, these observational data from a highly selected group cannot directly be extrapolated to daily practice and further research should (also) prospectively focus on morbidity of LE and salvage surgery and local and distal control in continued organ preserving treatment of recurrent/residual rectal cancer in Watch and Wait.

PART II Patient perspective

Life expectancy of (colo)rectal cancer patients has increased substantially over the years in the Netherlands, exposing survivors more to long-term negative effects of rectal cancer and its treatment.[33,34] While survival has historically been the primary driver for treatment, quality of life and survivorship issues are now increasingly important.[35] Organ preservation is becoming widely adopted with the intention of avoiding surgical (long-term) morbidity while the oncological risk seems very limited.[1] Health-related quality of life (HRQoL) of non-operated patients is significantly improved compared to radical surgery.[36]

Patients are keen to avoid a permanent stoma and other anorectal, urinary and sexual dysfunction.[37] This is the main driver of the Watch and Wait concept of Habr-Gama. One study showed that almost half of patients would even take an oncological risk to prevent radical surgery and the associated long term dysfunction.[38] Another study showed that avoiding a

stoma is often a greater worry for patients than disease-free survival.[37] Based on input from patients, the STAR-TREC phase III trial randomizing between two organ preservation arms and a radical surgery arm was redesigned to a patient preference model; patients want to have the option to choose for organ preservation.[39] Similarly, the TESAR trial has added an observational registration arm for patients who underwent local excision for low-risk T1 tumor, avoiding possible randomization to radical surgery.[40] Even when a patient experiences a regrowth, many are still interested in organ preserving options. In chapter V we show that patients who enter Watch and Wait but eventually require TME surgery, do not regret their decision. It is therefore imperative to understand the patient's perspective, which is often different from our own. A recent study showed that, although patients would take a risk to prevent surgery, almost half would not undergo a more toxic neo-adjuvant regimen to improve the chance of a cCR.[38]

Understanding the patient perspective will help to improve patient care. We can inform the patients better of risks and benefits they consider important and what the different treatment options could bring. This increased focus on functional problems and quality of life should continue after the treatment, during follow up, where attention should be focused on issues reported by patients themselves. For example, an important challenge for long-term rectal cancer survivors is not worry for cancer, but ostomy management.[35] In addition to trying to avoid major surgery with an organ preservation approach, it is worthwhile further studying how to avoid stomas and stoma problems in patients who still require TME surgery. In chapter VI we show that early closure of a diverting stoma does not improve HRQoL and we discuss how a diverting stoma can be avoided. The IMARI trial is now investigating a multi-interventional program to prevent and better treat anastomotic leaks in rectal surgery, without a stoma.

PART III Survey response assessment

In healthcare, important policy decision making and allocation of resources is often based on questionnaires. For example, DELPHI rounds provide information on the value of the ERAS protocol in surgery and to evaluate the nationwide implementation of such a program.[41,42] Although important, the reliability of the outcome of surveys depends on many factors. The summation of all forms of survey error in data collection is known as the 'Total Survey Error' and includes sampling variability, interviewer effects, response bias and frame errors.[43] An important factor is the response rate, which can lead to (non)response bias and influence other forms of survey error such as sampling and measurement issues. This is particularly important in healthcare, where patients with health problems participate less often than healthy people, leading to bias with underrepresentation of disease burden.[44] Response rates have been declining in the last 30 years likely due to a high survey exposure, a general decline in volunteerism in society and increasing difficulty in completing surveys (more follow-up, consent forms, additional measurements).[44] Response rate depends on many factors and even its definition is highly variable, illustrated by the fact that most journals have no guideline for reporting of response rates.[45,46] The American Association for Public Opinion Research

(AAPOR) has published standard definitions for survey response identifying 6 'participation rates'.[44,46] Although survey response depends on many factors that we cannot consequently guide by design, there are aspects we can influence to optimize survey response. In chapter VII and VIII we report that survey response depends on survey mode, follow-up, interviewee and patient characteristics. For optimal response, several aspects of survey design are key. A first important item is adequate selection of the target audience. Does one approach all patients after rectal surgery, or only men below 80 years of age still living at home? Proper selection will lead to a firmer conclusion as well as a higher and more predictable response rate. It is well known that physicians participate less often than patients, men less often than women, and that higher educated, married or working people respond more often than their counterparts.[44] In chapter VIII we show that for patients with colorectal diseases, a malignant diagnosis will negatively affect response rate.
The second item is the survey itself. In essence, it needs to be salient and should require little effort to complete.[47] Depending on the desired outcome, the design needs to take wording, length of questions, number of questions and proportion of open questions into account. Factors such as social desirability, especially in sensitive topics such as sexuality, can substantially affect responder outcome.
The next important item is the delivery of the survey. In chapter VII we show that personal interviews perform better than postal surveys, which by itself perform better than online surveys. Dillmann designed the Total Design Method for survey delivery with attention to administrative detail. This multi-step program ensures the highest response rates in postal and telephone surveys, and is validated in the Netherlands.[48] One of the important features is to claim importance through personalized registered post and minimizing participant effort by including stamped return envelopes. In chapter VIII we show that the popularity of internet surveys is rising. Although they require little effort, there is an over-abundance of online surveys that appear less important than a personally written survey delivered by registered post, resulting in low response rates.

The best of all worlds could be mixed-mode design, offering several advantages. An online option followed by a postal survey has similar overall response to a postal only option, but is less expensive than a postal survey to all.[49] Mixing modes can also improve response rate by allowing respondents to choose which mode they prefer.[49] Finally, by offering more survey modes sampling error can be reduced. For example, younger respondents may prefer an online option while older respondents may prefer a postal option.[50]
The 'how' of mixed mode design is still being investigated. Sequential administration of a mixed mode survey may lead to a higher response rate in certain groups than a concurrent design, as the latter might increase 'difficulty' by offering a choice of mode.[49,50] This is known as the 'choice paradox' in doctor surveys, for whom effort is an important factor in survey response.[51] Then there is timing; within 4 weeks the interval probably does not affect response rate, but it could influence which modality is chosen and thereby the costs.[52] Finally, there is the measurement error across modes; a respondent may answer differently to an interviewer

than in a self-administered online survey. Or, online auditory scales might be interpreted differently than visual printed scales in a paper survey. Similarly, multiple survey errors can occur when comparing unimodal versus mixed mode surveys, although some research suggests that this effect is limited.[53] Thus, mixing modes can threaten the comparability between studies.

Introducing a mixed mode design can cut costs, improve response rates and limit bias, but at the same time introduce other forms of survey error.[53,54] Declining response rates highlight the importance of further innovation. For one, further research will define the 'how' of mixed mode interviewing in the field of surgical survey research. It is essential to clarify what question the survey will answer, select a homogeneous target audience, administer the appropriate (mix of) survey modes and uniformly report outcome to minimize the Total Survey Error.

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APPENDICES

ENGLISH SUMMARY

PART I Surgical perspective

True complete responders in Watch and Wait have excellent oncological and improved functional outcome compared to surgery. Chapter II evaluates the outcomes of patients who 'fail' Watch and Wait in a retrospective cohort of 94 patients. Patients who undergo delayed TME surgery do not have an increased risk of readmission (10.0% vs 27.6%), surgical re-interventions (3.4% vs 15.0%) or stoma (31.0% vs 52.6%) in comparison to immediate surgery. Delayed surgery appears oncologically safe with 2-year overall survival of 100% and disease-free survival 81% while hospital costs are comparable (€13769 vs €11913). Therefore, it appears that repeated assessment to identify all true complete responders, does not 'harm' those that do not turn out to be a complete responder. Chapter III examines the role of local excision for suspected regrowth in the Dutch Watch & Wait registry. Many patients will favor organ preservation, even in the light of possible tumor regrowth. In 77 patients, local excision leads to continued organ preservation in 63% and colostomy-free survival in 68% of patients. It appears to be safe with overall survival of 96% at 5 years while all re-regrowths (22%) could undergo salvage surgery with curative intent. So, LE can be considered as an alternative to TME for suspected regrowth in selected patients who wish to preserve their rectum or avoid colostomy in distal rectal cancer.

Low specimen lymph node count (LNC) is often seen after neoadjuvant chemoradiotherapy (CRT). Chapter IV determines the prognostic value of LNC and lymph node ratio (LNR) in rectal cancer after neoadjuvant chemoradiotherapy (CRT). In total, 458 patients from 71 centers were included. LNC is not considered a proxy of surgical prowess (after CRT) as it does not appear to associated with OS or DFS, nor is LNR when corrected for N-stage. However, a low LNR does select patients within N-stage with improved survival and therefore might be used to identify subgroups of node-positive patients with a favorable outcome.

PART II Patient perspective

Chapter V describes the patient perspective after delayed TME surgery in Watch & Wait. Quality of life questionnaires (QLQ-C30 and QLQ-CR29), Worry for Cancer scale and Decision Regret scale were completed by 33 patients who underwent immediate and 18 patients who underwent delayed surgery. Quality of life was not impaired in patients who underwent delayed surgery. Even though these patients experienced tumor regrowth, worry for cancer was similar in the delayed surgery group (10.8 vs. 14.0, $p = 0.21$) compared to the immediate surgery group. Regret to enter Watch and Wait for those who 'failed' and eventually underwent TME surgery was very low (12-16%). Therefore, from a quality of life perspective, we do not 'harm' those patients that will not reach a complete clinical response. These findings therefore, support a repeated response assessment strategy after CRTx for rectal carcinoma to identify all complete responders.

Use of stoma is associated with poorer functional outcome, but it is unclear whether early reversal of a stoma is beneficial. Chapter VI evaluates the timing of stoma closure after low anterior resection for rectal cancer in a prospective cohort of 38 patients. Timing of stoma

closure in days or 'early' stoma closure within 3 months does not improve LARS or Wexner score. Quality of life, measured through FIQL and EORTC QLQ-29, did not differ for closure within or after 3 months. Therefore, it is hypothesized that timing of stoma closure is not a major factor in functional outcome and hypothesized that other factors (such as the use of a stoma) are more important factors.

PART III (Survey) Response Assessment

A low response rate can introduce bias and represent poor design. However, data on mean response rate have been lacking. Chapter VII describes a systematic review on survey response rates in patient and doctor surveys in the field of surgery. After inclusion of 2579 studies, the mean response rate was 70% in 811 studies in patients and 53% in 1746 doctor surveys. Response rate depends on several factors. For one, survey response varies from 76% in postal surveys to 46% in web-based surveys. Patients responded significantly more often than doctors to surveys regardless of survey mode. Additional contacts significantly improve response rate in email and web-based surveys in doctors, but not in postal surveys. There is no uniform mean or adequate survey response rate to go by and response rate should be interpreted within context of these factors.

Chapter VIII analyzes surveys performed in colorectal surgery. As shown in chapter VII, survey mode and interviewee type influence response rate. In 128 included studies, patients with colorectal cancer have a lower mean response rate than patients with benign pathology (62.8% vs 75.5%). Postal reminders appear to positively influence response rate in postal patient surveys. Overall, survey response is declining. Therefore, it is important to address these factors such as diagnosis of malignancy when designing and reviewing colorectal surgical survey studies. Chapter IV reports on survey response in surgical education research. In total, 312 survey studies involving surgical residents and medical students are included. The mean response rate is 55.7% for surgical residents and 69.0% for medical students. Educational surveys are increasing and most studies are web-based (n = 166, 53.2%), although they yield the lowest response rate (mean 52.6%). The comparison of survey studies is difficult, because of unclear and inconsistent reporting of the methods used. Therefore, we present an initial 17 point reporting guideline in order to provide a framework for surveys in surgical education.

NEDERLANDSE SAMENVATTING

DEEL I Chirurgisch perspectief

Echte complete responders met niet operatief beleid hebben uitstekende oncologische en betere functionele resultaten in vergelijking met chirurgie. Hoofdstuk II evalueert de uitkomsten van patiënten die Watch and Wait 'falen' in een retrospectief cohort van 94 patiënten. Patiënten die een uitgestelde TME-operatie ondergaan, hebben geen verhoogd risico op heropname (10.0% vs. 27.6%), chirurgische herinterventies (3.4% vs 15.0%) of stoma (31.0% vs 52.6%) in vergelijking met direct chirurgie na voorbehandeling. Uitgestelde chirurgie lijkt oncologisch veilig met een 2-jaarsoverleving van 100% en een ziektevrije overleving van 81%, terwijl de ziekenhuiskosten vergelijkbaar zijn (€ 13769 vs € 11913). Daarom lijkt het erop dat herhaalde beoordeling om alle echte complete responders te identificeren, degenen die geen complete responder blijken te zijn, niet 'schaadt'.

Hoofdstuk III onderzoekt de rol van lokale excisie bij vermoedelijke lokale terugkeer van ziekte in het Nederlandse Watch & Wait register. Veel patiënten zullen de voorkeur geven aan orgaanbehoud, zelfs in het licht van mogelijke lokale terugkeer van ziekte. Bij 77 patiënten leidt lokale excisie (LE) bij 63% van de patiënten tot behoud van orgaanpreservatie en bij 68% tot overleving zonder stoma. Het lijkt een veilige behandeloptie te zijn met een algehele overleving van 96% na 5 jaar, terwijl alle patienten met lokale terugkeer van ziekte (in 22% van de gevallen) alsnog een radicale operatie kunnen ondergaan met intentie van genezing. LE kan dus worden beschouwd als een alternatief voor radicale chirurgie voor vermoedelijke lokale terugkeer van ziekte bij geselecteerde patiënten die hun rectum willen behouden of stoma willen vermijden.

Een laag aantal lymfeklieren (LNC) wordt vaak gezien in het preparaat na neoadjuvante chemoradiotherapie (CRT). Hoofdstuk IV bepaalt de prognostische waarde van LNC en lymfeklierratio (LNR) bij rectumkanker na neoadjuvante chemoradiotherapie (CRT). In totaal werden 458 patiënten uit 71 centra geïncludeerd. LNC wordt niet beschouwd als een afgeleide van chirurgische bekwaamheid (na CRT) omdat het niet blijkt geassocieerd met OS of DFS. Hetzelfde geldt voor LNR, ook na correctie voor N-stadium. Een lage LNR selecteert echter patiënten binnen het N-stadium met betere overleving en kan daarom worden gebruikt om subgroepen van klier-positieve patiënten met betere overleving te identificeren.

DEEL II Patient perspectief

Hoofdstuk V beschrijft het patiëntperspectief na uitgestelde TME-chirurgie in Watch & Wait. Kwaliteit van leven-vragenlijsten (QLQ-C30 en QLQ-CR29), Worry for Cancer-schaal en Decision Regret-schaal werden ingevuld door 33 patiënten die onmiddellijk werden geopereerd en 18 patiënten die een uitgestelde operatie ondergingen. De kwaliteit van leven was niet verminderd bij patiënten die een uitgestelde operatie ondergingen. Hoewel deze patiënten een terugkeer van lokale ziekte ondervonden, was de angst voor kanker vergelijkbaar met de groep die onmiddelijke chirurgie onderging (10.8 vs. 14.0). Spijt om mee te doen aan Watch

and Wait, voor degenen die uiteindelijk toch een TME-operatie ondergingen, was erg laag (12-16%). Daarom 'schaden' we die patiënten die geen volledige klinische respons zullen bereiken, vanuit het perspectief van kwaliteit van leven, niet. Deze bevindingen ondersteunen daarom een herhaalde responsbeoordelingsstrategie na CRTx voor rectumcarcinoom om alle complete responders te identificeren.

Het gebruik van een stoma gaat gepaard met een slechter functioneel resultaat, maar het is onduidelijk of het vroegtijdig herstellen van een stoma gunstig is. Hoofdstuk VI evalueert de timing van het sluiten van het stoma na een lage anterieure resectie voor rectumkanker in een prospectief cohort van 38 patiënten. Tijdstip van stomasluiting in dagen of 'vroege' stomasluiting binnen 3 maanden verbetert de LARS- of Wexner-score niet. Kwaliteit van leven, gemeten via FIQL en EORTC QLQ-29, verschilde niet voor sluiting binnen of na 3 maanden. Daarom wordt verondersteld dat het tijdstip van het sluiten van de stoma geen belangrijke factor is in de functionele uitkomst en dat andere factoren (zoals het gebruik van een stoma) belangrijker zijn.

Deel III (Vragenlijst) respons analyse

Een laag responspercentage kan leiden tot bias en het gevolg zijn van suboptimaal studie ontwerp. Data over de gemiddelde responspercentages in ontbreken echter. Hoofdstuk VII beschrijft een systematische review over de responspercentages van enquêtes in patiënten- en artsenenquêtes op het gebied van chirurgie. Na inclusie van 2579 studies, blijkt het gemiddelde responspercentage 70% in 811 onderzoeken bij patiënten en 53% in 1746 artsenenquêtes. Het responspercentage is afhankelijk van verschillende factoren. Ten eerste varieert de respons van 76% in enquêtes per post tot 46% in webgebaseerde enquêtes. Patiënten reageerden significant vaker dan artsen op enquêtes, ongeacht het type enquête. Herhaald contact verbetert het responspercentage in e-mail en webgebaseerde enquêtes bij artsen aanzienlijk, maar niet in postenquêtes. Er is geen uniform gemiddeld of adequaat responspercentage voor enquêtes te duiden; het responspercentage moet worden geïnterpreteerd in de context van deze eerder genoemde factoren.

Hoofdstuk VIII analyseert studies uitgevoerd in de colorectale chirurgie. Zoals aangetoond in hoofdstuk VII, wordt het responspercentage beïnvloed door het type enquête en wie je interviewt. In 128 geïncludeerde onderzoeken hadden patiënten met colorectale kanker een lager gemiddeld responspercentage dan patiënten met goedaardige pathologie (62.8% versus 75.5%). Herinneringen per post lijken een positieve invloed te hebben op het responspercentage in patiëntenenquêtes per post. Over het algemeen neemt deelname aan enquêtes af. Daarom is het belangrijk om deze benoemde factoren, zoals de diagnose van maligniteit, mee te wegen bij het ontwerpen en beoordelen van colorectale chirurgische enquête studies. Hoofdstuk IV rapporteert over de respons op enquêtes in chirurgisch onderwijsonderzoek. In totaal zijn 312 enquêtestudies met chirurgische artsen in opleiding en medische studenten opgenomen. Het gemiddelde responspercentage is 55.7% voor chirurgische artsen in opleiding en 69.0% voor medische studenten. Onderwijsenquêtes nemen toe in aantal en de meeste onderzoeken zijn webgebaseerd (n = 166, 53.2%), hoewel

dit type de laagste respons oplevert (gemiddeld 52.6%). Het vergelijken van enquête studies is moeilijk vanwege onduidelijke en inconsistente rapportage van de gebruikte methoden. Daarom presenteren we een 17 punts rapportagerichtlijn om een kader te bieden voor enquêtes in chirurgisch onderwijs.

IMPACT

Scientific Impact

The aim of this thesis is to assess the outcomes of (new) treatments in rectal surgery, especially for patients who will require surgery. These are divided in three parts; 1] oncological and surgical outcome from a surgeon's perspective, 2] functional outcome and quality of life from a patient's perspective and 3] evaluation of survey response to aid in improvement of evaluation of care.

The most important results and conclusions are [1] hospital costs, oncological and surgical outcome are not impaired for those patients who require delayed radical surgery for a regrowth in a Watch and Wait strategy; [2] patients who require delayed surgery have no impaired quality of life or worry for cancer compared to immediate TME and have no decision regret regarding their initial choice for Watch and Wait; [3] local excision appears to be a safe option for a number of patients who wish to continue organ preservation or avoid a stoma in case of suspicion of regrowth; [4] lymph node count is not prognostic after chemoradiotherapy for rectal cancer and should not be a quality parameter; [5] reversal of loop ileostomy after rectal resection within 3 months does not improve bowel function or quality of life; [6] many factors influence the mean survey response, with some factors specific for colorectal surgery surveys; [7] a concise guideline is proposed for reporting of surveys in surgical education research. Conclusions [1-3] show that patients in a Watch and Wait strategy who experience regrowth are not harmed, adding to the scientific base for Watch & Wait. Conclusions [6-7] provide a reference for survey design and review in order to improve survey quality.

Social Impact

The relevance of this thesis is in the clinical application for the treatment of rectal cancer patients. Patients with a major or good response to neo-adjuvant therapy can potentially avoid major surgery and the associated short- and long-term morbidity. Patients are highly interested in trying to maintain a high quality of life by avoiding a permanent colostomy and/or long term anorectal and urogenital dysfunction. With the findings in this thesis patients and doctors are better informed on functional, surgical and oncological outcome of a Watch and Wait approach, especially in those patients who still require surgical treatment for a regrowth. These findings are not only of interest for surgeons, but also for gastro-enterologists, oncologists, radiologists, pathologists, physicianassistants and general practitioners involved in care for rectal cancer patients. Finally, part III of this thesis will provide reference for researchers in rectal cancer surgery to interpret and value survey
response and also aid in survey design which will improve survey quality that eventually might improve outcome in rectal cancer surgery.

Activity

Watch and Wait has become a valid treatment option that is incorporated in the revised Dutch colorectal cancer guidelines, for a large part because of the activities of the 'Dutch Wait and See' network, created through the implementations study funded by the Dutch Cancer Society and coordinated by the Netherlands Cancer Institute. Patients can get information through their own doctor, as well as through the guidelines and patient organizations. Through the expanding number of hospitals in the 'Dutch Wait and See' network, patients can find information on hospital websites and leaflets. There are regular activities and meetings focused on patients and healthcare professionals in the Netherlands Cancer Institute/Antoni van Leeuwenhoek, as well as in other centres. For the health care professionals the meetings present all new developments and research findings in W&W, and new research opportunities are discussed. These meetings serve to promote and implement new knowledge and treatment strategies for the benefit of patients throughout The Netherlands.

It is of note that the data of part I and II of this thesis is largely derived from national registries, such as the SNAPSHOT and Dutch Wait and See databases. These registries are supported directly and indirectly by funds from government, Dutch Cancer Society and individual hospitals and are highly valuable tools for clinical research. Together with the unique collaborative mindset of the Dutch surgeons, The Netherlands have become leading in multicenter and registry-based prospective research. The field of non-operative treatment in rectal cancer is a good example, where The Netherlands is internationally recognized as a frontrunner with innovative clinical studies. Ongoing funding and collaborative work remains important to keep moving the field forward, to the benefit of patients.

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ABOUT THE AUTHOR

Vincent Maurice Meyer was born on March 15th, 1988, in Roden, The Netherlands. He graduated from Willem Lodewijk Gymnasium secondary school in Groningen in 2006. The same year he started his medical degree at the University of Groningen, with an additional clinical internship in Masaka, Uganda and a research internship in Visual Neuroscience at the University Medical Center Groningen. In autumn 2013, he received his medical degree from the University of Groningen. Subsequently he worked for one year as a surgical resident not in training in the University Medical Center Groningen. Afterwards, he moved to Dublin, Ireland to gain clinical experience abroad. In January 2015, he started work as a senior house officer (SHO) in the Emergency Department of St. Vincent University Hospital in Dublin and contributed to research on head injury with Prof. Ryan. In this Emergency Department he met his colleague and future wife, Gillian. Following this, he continued with rotations in Orthopedic Trauma Surgery and Hepatobiliary Surgery in St. Vincent University Hospital. After 18 months, Vincent and Gillian returned to the Netherlands in 2016 where Vincent worked as a surgical resident in Martini Hospital, Groningen and started his research on surgical questionnaires with dr. Lange and dr. Pol in University Medical Center Groningen. In September 2017 he started his surgical residency in Isala Hospital, Zwolle. He started as a PhD candidate at Maastricht University (GROW) and the Isala Hospital at the Department of Surgery in 2019 under supervision of dr. van Westreenen, dr. de Vos tot Nederveen Cappel and prof. Beets, focusing on recurrence in Watch & Wait for rectal cancer. He postponed surgical training for 5 months in 2020 for fulltime research, for which he received a research grant by the Innovation & Science board of Isala Hospital. During his PhD, he presented at national and international conferences and was awarded the 'Workhorse' award in Isala Hospital. He is currently continuing his surgical residency program in the University Medical Center Groningen.

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Marc, BB, 'go to guy'. Als er wat is, ben je er. Piano zeulen door centrum Zwolle, of een bed de Radesingel op. Volgens mij heb je me 9x verhuisd. Ook altijd trots als er een artikel gepubliceerd is. Ik zeg het niet zo vaak, maar dank dat ik op je kan bouwen.

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