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Chapter 6:

OPTIMAL TREATMENT STRATEGY IN RECTAL CANCER SURGERY; SHOULD WE BE COWBOYS OR CHICKENS?

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Abstract

Introduction: Surgeons and hospitals are increasingly accountable for their postoperative complication rates. This may lead to risk-averse treatment strategies. It is not known whether a risk-averse strategy leads to providing better care. The aim of this population-based study was to determine the association between hospitals' strategy regarding defunctioning stoma construction and postoperative outcomes in rectal cancer surgery.

Methods: Data of the Dutch Surgical Colorectal Audit including 3104 patients undergoing rectal cancer resection and receiving an anastomosis between January 2009 to July 2012 in 92 hospitals were used. Hospital variation in defunctioning stoma rates was calculated as an observed (O) versus expected (E) rate, adjusted for relevant case-mix factors. Anastomotic leakage and 30-day mortality rates were compared in hospitals with high and low tendency towards stoma construction.

Results: Seventy-six percent of all patients received a defunctioning stoma; 9.6% of all patients developed anastomotic leakage. Postoperative mortality was 1.8%. Hospitals' adjusted proportion of defunctioning stomas varied from 0-100%. There was no significant correlation between hospitals' adjusted stoma O/E rate and anastomotic leakage rate. Severe anastomotic leakage rates were similar (7.0 versus 7.1%, p=0.95) in hospitals with the lowest and highest stoma rates. Mild leakage and postoperative mortality rates were higher in hospitals with high stoma rates.

Conclusion: A high tendency towards stoma construction in rectal cancer surgery did not result in lower overall anastomotic leakage or mortality rates. It seems that not a risk averse strategy, but the ability to select patients for stoma construction is the key towards preferable outcomes.

Introduction

Surgical resection is the cornerstone of rectal cancer treatment. If tumour size, stage and location allow for a sphincter preserving resection, and bowel continuity is restored, the surgeon has to decide whether or not to defunction the anastomosis. This decision concerns the trade-off between benefit and harm. The advantage of a defunctioning stoma can be that it decreases the consequences of anastomotic leakage, and may also decrease its incidence.[1;2] Anastomotic leakage is a serious complication causing re-operation, prolonged hospital stay, morbidity, mortality, and possibly worse oncological outcome.[3-5] On the other hand a stoma has evident disadvantages; defunctioning stomas can induce morbidity, discomfort (decreased quality of life), higher costs[6], longer hospitalisation[7] and even mortality from surgery to close the stoma. [8-12] Furthermore, 80% of defunctioning stomas is only reversed after 4 months and 20 % is never reversed.[13]

Nowadays quality of care has become a major topic and surgeons and hospitals are increasingly accountable for their postoperative complication rates. This may lead to risk averse treatment strategies. Previous research suggests that differences in professional opinion may lead to variation in health care delivery.[14-21] The threshold for the decision to construct a stoma to avoid the risk for anastomotic leakage may also vary between surgeons. Some surgeons may be more risk-taking or risk-averse than others. However, the attempt to avoid or limit the risk for anastomotic leakage after colorectal surgery by frequent use of stomas is only in patients' interest if it in fact lowers clinically relevant anastomotic leakage and mortality rates.

The objective of this study was to investigate whether hospitals differ in their treatment strategy regarding construction of defunctioning stomas in rectal cancer surgery, and to assess if a hospital's treatment strategy is related to its postoperative outcomes such as clinically relevant anastomotic leakage and mortality rates.

Methods

Study cohort

Data was derived from the Dutch Surgical Colorectal Audit (DSCA), a national quality improvement project in which over 200 variables concerning the patient, co-morbidity, diagnostics, disease-specific details, treatment, and outcomes are collected prospectively. The DSCA contains data registered by 92 hospitals (representing all hospitals performing colorectal cancer surgery in the Netherlands). Over 90% of all eligible patients are included. The dataset is disease-specific for colorectal cancer and has shown a nearly 100% concordance on most items upon validation against the Netherlands Cancer Registry dataset.22 All patients having undergone anterior resection for primary rectal cancer between the 1st of January 2009 and 31st of July 2012 were evaluated. Minimal data requirements for inclusion in the analysis were: information on tumour location, date of surgery, and mortality. Patients without an anastomosis, with metastasis at time of primary surgery, resections for multiple synchronous colorectal tumours, and patients with a tumour less than 5 cm from the anal verge were excluded, because these represent subgroups of patients with specific treatment perspectives and subsequent different expected outcomes.

Definitions

Overall anastomotic leakage, as used in the hospital comparisons, was defined as 'clinically relevant anastomotic leak requiring a re-intervention, either radiological (mild) or surgical (severe)'. Postoperative mortality was defined as 'in-hospital mortality or all deaths within 30 days after primary surgery'.

The following casemix factors were considered: age, gender, ASA-classification, abdominal surgical history, tumour height, preoperative tumour complications, and urgency of the resection.

Considered treatment factors were surgical procedure (laparoscopic or open), and the use of neoadjuvant treatment.

Hospitals were stratified into two categories: non-teaching and teaching hospitals. A teaching hospital is a hospital, which provides medical training to surgical residents. Procedural volume in rectal cancer resections was calculated for each hospital before the aforementioned exclusion of patients. Hospital volume was categorized into <25, 25–50 and >50 resections per year.

Statistical considerations

As patient and tumour related case-mix factors may be responsible for a large part of the hospital variation in the number and proportion of patients with a defunctioning stoma, we adjusted for these differences by calculating the Observed/Expected (O/E) stoma rate. For this calculation, the observed outcome was the number of patients with a defunctioning stoma in a hospital and the expected outcome is the sum of all patients' estimated probabilities for a defunctioning stoma. Patients' probability estimates were derived from a backwards-stepwise multivariate logistic regression model, fitted on the data of all included hospitals, and using all case-mix factors mentioned above. For an average performing hospital, the observed outcome will be equal to the expected outcome, resulting in an O/E outcome ratio of 1. Hospitals that construct more defunctioning stomas than average have an O/E outcome ratio higher than 1, while this ratio is lower than 1 in hospitals with lower than average stoma rates.
Next, the adjusted hospitals O/E ratios for strategy (stoma use) were plotted against their anastomotic leakage rates.

The relation between the hospitals' strategy and its outcomes was analyzed by two methods. First, to evaluate whether stoma rates were related to (lower) anastomotic leakage rates on a hospital level, a linear correlation was calculated using Pearson's correlation coefficient R. Second, to evaluate whether a risk averse strategy (high stoma rates) is related to better postoperative outcomes on a hospital level, hospitals were grouped into equally-sized groups based on quintiles of their case-mix adjusted rate of defunctioning stomas. Differences between groups in outcomes (mild and severe anastomotic leakage and mortality rates) were analyzed using a chi-square test.

The association of patient and tumour related case-mix factors, hospital factors (teaching status, volume) and treatment factors (neoadjuvant therapy, laparoscopic surgery) with being in the high stoma group was assessed with a chi-squared test and multivariate logistic regression analysis, considering the same case-mix factors as mentioned above All statistical analyses were performed in PASW Statistics, Rel. 18.0.2009. Chicago.

Results

Between January 1 2009 and July 31 2012, 92 hospitals registered all rectal cancer patients in de the DSCA. After exclusion of ineligible patients, a total of 3104 patients were included in the analysis. Characteristics of the included patients and hospitals are shown in Table 1.Of all patients, 67% (n=2080) received an anastomosis with a defunctioning stoma.

In total, 302 patients (9.6%) developed anastomotic leakage. The majority (187 of 302, 62%) were severe leakages requiring a surgical reintervention. Anastomotic leakage rates were somewhat higher in patients with a defunctioning stoma (9.3 versus 10.4%), but this difference was not statistically significant (p=0.35). Fifteen of 302 patients that developed anastomotic leakage, died during hospital stay or within 30 days after surgery (5%). Overall postoperative mortality rate was 1.8% (n=187); anastomotic leakage caused one-fourth of overall mortality.

Hospitals

Relevant casemix factors were selected by backward stepwise logistic regression analysis. Relevant factors for the proportion of defunctioning stomas were gender, preoperative complications, tumour location, and laparoscopic surgery.

Hospitals' unadjusted proportion of defunctioning stomas varied considerably: percentages ranged from 0-100% (*figure 1*). *Figure 2* shows the relation between the hospitals' adjusted proportion (O/E ratio) of defunctioning stomas and the hospitals' overall anastomotic leakage rate. Hospitals varied in anastomotic leakage rates (3-18%). There was a weak positive correlation between hospitals' adjusted O/E stoma ratio and anastomotic leakage rates (r=0.032), this was not statistically significant (p=0.76).

Low versus high stoma rate

Eighteen hospitals with a total number of 604 patients were identified as the group of low stoma rates. This group had a mean percentage of 26% of patients with a defunctioning stoma. The group of high stoma rates consisted of 18 hospitals, which treated 521 patients in total, had a 88% mean defunctioning stoma rate (*Figure 3*). A slight difference in overall anastomotic leak rates was found between groups, although not statistically significant (8.4 vs11.3%, p=0.11). Severe anastomotic leakage rates were similar in both groups; 7.1 versus 7.5% (p=0.95). Mild anastomotic leakage rates were significantly higher in the group with high stoma rates: 1.5 versus 3.8% ($p<0.001$). Postoperative mortality rates were significantly higher in the group with high stoma rates; 2.9 versus 1.0% (P=0.02). The remaining hospitals formed a group with intermediate stoma rates (67%), and had outcomes in between the low and high stoma groups (9.7% anastomotic leakage, 1.7% mortality).

Table 2 shows the results of univariate and multivariate analysis for factors contributing to the odds of being in the group of high stoma rates. The percentage of patients treated with short course radiation therapy (SCRT) was higher in the group with high stoma rates, as well as the percentage of patients treated in teaching hospitals. Also in multivariate analysis, these patients had higher odds of being in the group of high stoma rates. Urgent resections and volume were associated with a lower risk of being treated in a high stoma rate hospital in both univariate and multivariate analysis (*Table 2*). Other case-mix factors, as age, ASA score and tumor characteristics, were not statistically different in both groups.

Discussion

Overview of findings

This study demonstrates a large hospital variation in treatment strategy concerning defunctioning stoma construction after surgical resection of rectal cancer, even after adjustment for relevant casemix factors. Hospitals with a low threshold for defunctioning stoma construction after rectal cancer resection did not have lower anastomotic leakage rates in comparison with hospitals with an opposite strategy. Interestingly, mortality and anastomotic leakage rates requiring radiological drainage were even higher in hospitals with a high stoma rate. The latter may be partly due to the slight difference in short course radiation therapy (SCRT) between both groups. Although a direct correlation between clinically apparent anastomotic leakage and neoadjuvant therapy has not been demonstrated,[4;23-26] den Dulk et al showed SCRT to be a limiting factor for reversal of a (secondary) constructed stoma suggesting that it increases the risk for subclinical, or mild anastomotic leakage.[27]
An explanation for the remarkable correlation between a risk averse strategy and low hospital volume or teaching status cannot be provided within the scope of this article. Possibly, these hospitals may use other selection criteria for defunctioning stomas, or treat patients with an

impaired condition for which could not be adjusted in this study.

Comparison with other studies

There is an on-going debate on differences in treatment approach despite ample data describing the direct correlation between the rate of both defunctioning stomas on the one hand, and anastomotic leakage and postoperative mortality on the other hand. The discussion focuses mainly on whether defunctioning stomas should be used routinely after low anterior resection to decrease anastomotic leakage rates. A meta-analysis from Hüser et al1, mainly based on the results of a randomized controlled trial from Mathiessen et al2 clarifies the advantage of a defunctioning stoma on lowering anastomotic leakage rates. This is confirmed by a considerable amount of retrospective studies.[4;28-30] On the contrary, a study from Fielding et al. observed a higher leakage rate in patients with a defunctioning stoma (18% versus 7%) and suggested that surgeons with an individual anastomotic leakage rate less than 5% do not need to create a defunctioning stoma at all. Both Enker et al, and Matthiessen et al. showed that a defunctioning stoma did not reduce the incidence of anastomotic leakage in patients undergoing low or ultralow anterior resection.[7;31] Nevertheless, it has been agreed previously that there is a need for a benchmark on hospitals' defunctioning stoma and anastomotic leakage rates.

Strengths and limitations of study

We retrospectively evaluated a prospectively maintained, population-based database to determine the association between hospitals' strategy regarding defunctioning stoma construction and postoperative outcome in rectal cancer. It could be argued that comparing patient outcomes for patients with and without a stoma is not valid, because of confounding by indication: patients may have received a stoma because they were considered to be high risk patients and are therefore not comparable to patients that did not receive a defunctioning stoma. This bias could also explain the relatively high mortality in the group with high stoma rates. However, in our study this bias is largely overcome by comparing hospitals at both ends of the spectrum (either very high or very low defunctioning stoma rates). Defunctioning stoma rates of 88% and 26% respectively, reflect a strategic approach (standard a stoma or standard no stoma), that is only slightly based on individual decision making concerning patient characteristics. It is likely that only very high risk patients received a stoma in both groups, and very low risk patients in both groups did not. For other patients, the decision was mainly based on the hospitals strategic approach. Therefore the method we used in our study resembles a "pseudorandomisation". This is supported by the fact that baseline characteristics were similar for both groups in our study.

The findings of this study are very useful for clinical practice because they strengthen the concept that the decision of stoma formation after anterior rectal resection cannot be standardized but require a careful evaluation of individual risk factors. Data represent current surgical practice at a population level, since all hospitals participate in the DSCA and the percentage of eligible patients registered is over 90%.

A limitation of this study is that analyses were performed at a hospital level, while the surgical strategy may differ between surgeons within a hospital. Information on a surgeons' level is not available in the DSCA and individual volumes may be low, introducing more impact of chance variation in the analyses.

Clinical implications

Should we then be cowboys or chickens; if the latter does not necessarily result in better outcomes? The results confirm that the protective effect of a defunctioning stoma is probably most apparent in high-risk patients, while the additional benefit for the rest of the population is limited or even non-existent. There have been numerous studies identifying risk factors for anastomotic leakage. [9-13] Dekker et al developed and tested the Colon Leakage Score (CLS) in which multiple risk factors were used to provide an objective prediction of the risk for anastomotic leakage.[32] They found that only 20% of their population could be considered as high risk. If we take into account the relative risk reduction of 64% that was found in the randomized trial of Matthiessen et al. (reduction in AL from 28% to 10%) for high-risk patients with lets say an a priori risk of anastomotic leakage of 20%, this would mean an absolute risk reduction of 12.8% and so 8 defunctioning stomas would have to be constructed in order to prevent one anastomotic leak. In contrast, for patients with an a priori risk of 5%, (ARR 3.2%) 31 defunctioning stomas would have to be created to prevent one leak.

It should thereby kept in mind that stomas can induce morbidity, discomfort (quality of life), costs and even mortality. Stomal complications cause re-admission within two months after initial surgery in up to 17% of all patients, mostly due to de-hydratation[9;11;33;34]. Even when a defunctioning stoma is constructed, there is still is a considerable risk of (late) anastomotic leakage [2;4;35-37] It is also recognized that 15-30% of defunctioning stoma's are never closed, resulting in a permanent stoma[10;38]

Future multicentre randomised trials are important to gain more evidence on the possible benefits of defunctioning stomas. However, in our opinion they can be only useful if they discriminate between high and low risk patients. Therefore, future studies should first focus on adequately identifying these patients, to prevent the creation of non-beneficial defunctioning stomas in low risk patients.

Finally, we advocate that patients' preferences concerning the risk of morbidity and mortality of anastomotic leakage versus the consequences of a defunctioning stoma should be taken into account preoperatively. This requires thorough preoperative counselling.

Conclusion

In conclusion, a high tendency towards defunctioning stoma construction in rectal cancer surgery did not result in lower overall anastomotic leakage or mortality rates. The optimal treatment strategy can probably be found in hospitals with both low stoma rates and favourable postoperative outcomes. It seems that hospitals with low stoma rates were better in selecting high-risk patients, and that stoma formation in more patients does not lead to better outcomes. Adequate identification of high-risk patients should be focus of future studies to facilitate decision-making.

Table 1. Patient, tumour and treatment characteristics of included patients. ASA: American Society of Anaesthesiologists risk score.

		N	***%***
Total			
Age	Mean (range)	66	(15-97)
Gender	Male	1850	60%
ASA classification	I-II	2567	83%
	III+	369	12%
	Missing	168	5%
Abominal surgical history	Yes	808	26%
Tumor location	>=10 cm	1149	14%
	<10 cm	1660	20%
Urgency	Acute/urgent	57	2%
Tumour stage	(Y) pT0/X	207	7%
	pT1	269	9%
	pT2	990	32%
	pT3	1533	49%
	pT4	105	3%
Surgical preoperative treatment	Stoma	162	5%
	Stent	8	0,30%
	Other	51	3%
Neoadjuvant treatment	5x5 Gy	1623	52%
	Chemoradiation	825	27%
Surgical procedure	Laparoscopic resection	1393	45%
Hospitals: type	Teaching hospital	2175	70%
	Non-teaching hospital	929	30%
Hospitals: volume	High volume (>50/year)	875	28%
	Medium volume (25-50 /year)	1490	48%
	Low volume (< 25/year)	739	24%

*Table 2: Univariate and multivariate analysis for factors contributing to being in the group of high stoma rates, *Odds ratios display the odds for being in the group of high stoma rates.*

Factor		***Univariate***		***Multivariate***	
		Cowboys n (%)	***Chickens n (%)***	***OR****	***95 % CI***
Age	mean	66	66	0.99	0,98 - 1.01
Gender	female	247 (41)	210 (40)	0.88	0,68 - 1.14
Asa	1	157 (30)	149 (30)	1.0	ref
	2	297 (56)	307 (60)	1.13	0.76 – 1.36
	3+	79 (15)	52 (10)	0.81	0.55 - 1.30
Urgency	urgent operation	**18 (4)**	**4 (0.8)**	**0.29**	**0.09 - 0.89**
Preopeative surgery	Yes	24 (4)	25 (5)	1.19	0.64 - 2.24
Tstage (p)	T0	22 (4)	32 (7)	1.0	Ref
	T1	53 (9)	55 (11)	1.35	0.36 - 5.00
	T2	193 (32)	165 (32)	1.02	0.29 - 3.61
	T3	314 (52)	260 (50)	1.08	0.31 - 3.78
	T4	22 (4)	9 (2)	0.62	0.14 - 2.74
Abdominal surgical history	yes	135 (22)	144 (28)	1.26	0.94 1.70
Tumour distance - anal verge	>10 cm	225 (37)	137 (33)	0.87	0.66 - 1.14
Neoadjuvant therapy	none	**171 (28)**	**100 (19)**	1.0	ref
5x5	5x5 gy	**301 (50)**	**308 (60)**	**1.67**	**1.20 - 2.31**
	chemoradiation	132 (22)	133 (22)	1.13	0.72 - 1.69
Surgical treatment	laparoscopy	291 (50)	286 (55)	1.09	0.84 - 1.41
Hospital type	teaching	**259 (43)**	**269 (52)**	**2.88**	**2.04 - 4.10**
Volume	<25	191 (32)	141 (27)	1.0	ref
	25-50	222 (36)	274 (53)	1.18	0.86 - 1.62
	>50	**191 (32)**	**106 (20)**	**0.27**	**0.17 - 0.43**

Bold printed numbers are statistically significant (p<0.05).

Figure 1. Hospitals ranked by their case-mix adjusted defunctioning stoma rate. Based on quintiles a group of low (left) and high (right) stoma rates was identified.

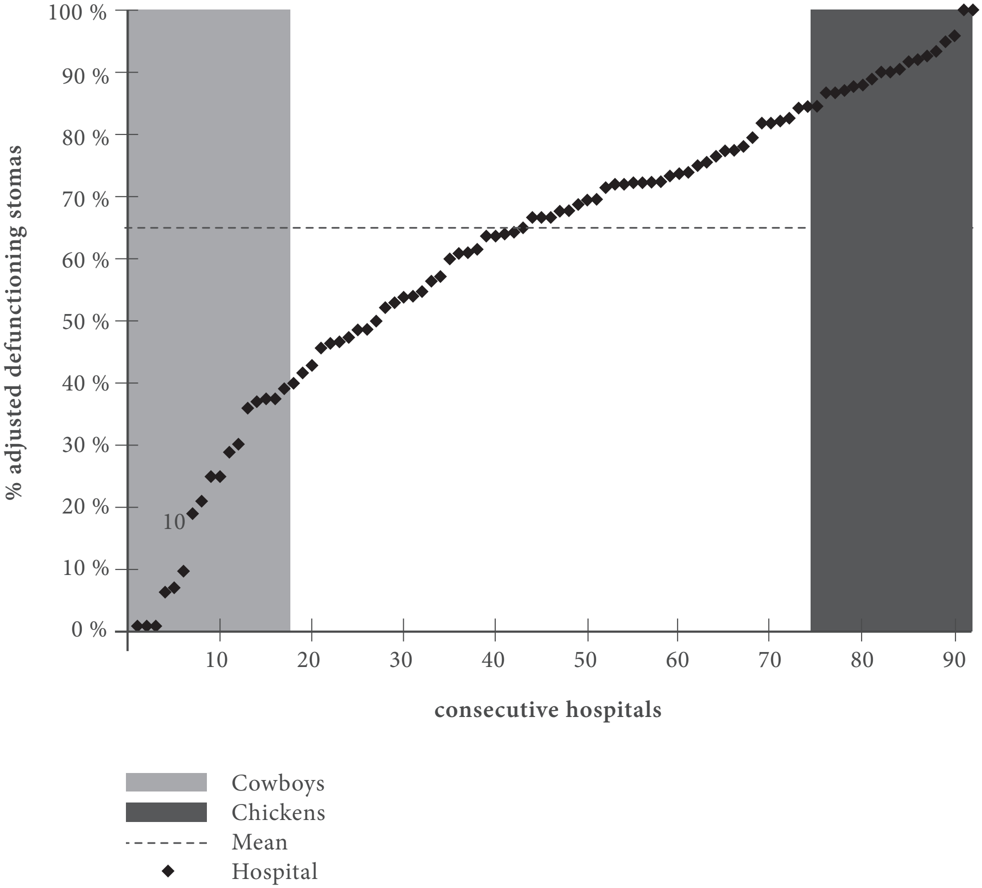


Figure 2. Hospitals' adjusted defunctioning stoma rates plotted against their anastomotic leakage rates.

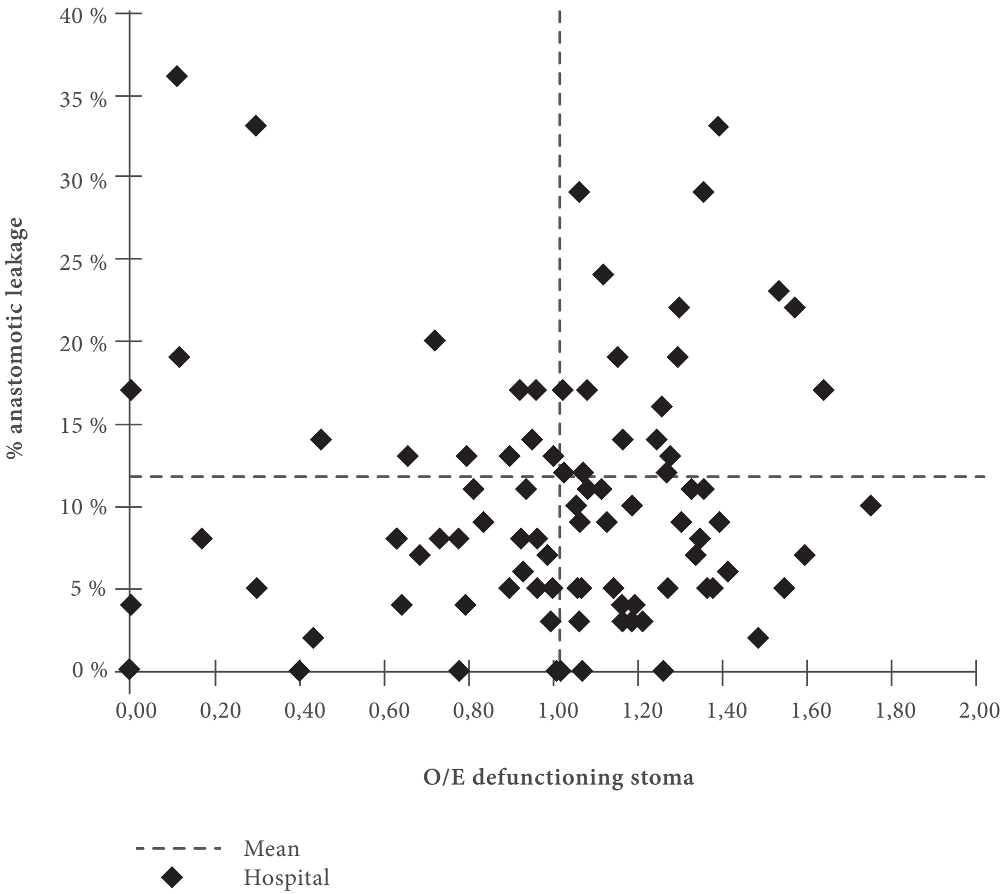
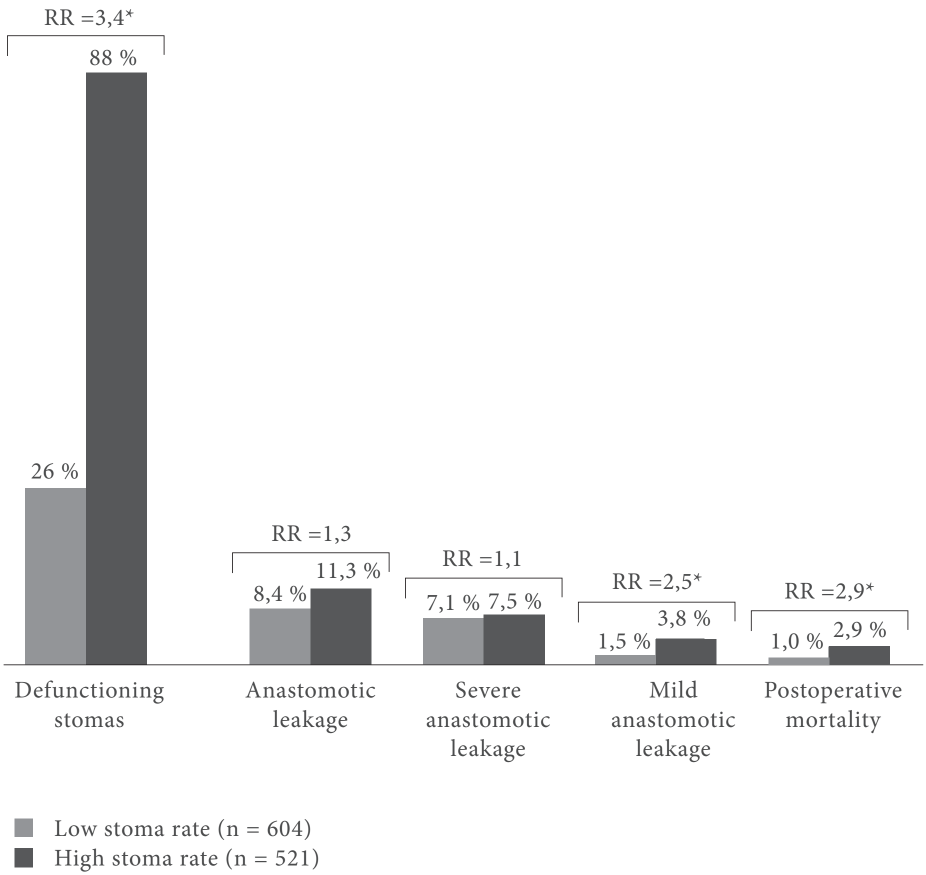


*Figure 3. Comparison of outcomes between groups identified as low and high stoma rates. Results with an * are considered statistically significant (P<0.05).*



REFERENCES

1. Huser N, Michalski CW, Erkan M, Schuster T, Rosenberg R, Kleeff J et al. Systematic review and meta-analysis of the role of defunctioning stoma in low rectal cancer surgery. Ann Surg 2008; 248(1):52-60.
2. Matthiessen P, Hallbook O, Rutegard J, Simert G, Sjodahl R. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg 2007; 246(2):207-214.
3. den Dulk M, Marijnen CA, Collette L, Putter H, Pahlman L, Folkesson J et al. Multicentre analysis of oncological and survival outcomes following anastomotic leakage after rectal cancer surgery. Br J Surg 2009; 96(9):1066-1075.
4. Peeters KC, Tollenaar RA, Marijnen CA, Klein KE, Steup WH, Wiggers T et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg 2005; 92(2):211-216.
5. Snijders HS, Wouters MW, van Leersum NJ, Kolfschoten NE, Henneman D, de Vries AC et al. Meta-analysis of the risk for anastomotic leakage, the postoperative mortality caused by leakage in relation to the overall postoperative mortality. Eur J Surg Oncol 2012; 38(11):1013-1019.
6. Koperna T. Cost-effectiveness of defunctioning stomas in low anterior resections for rectal cancer: a call for benchmarking. Arch Surg 2003; 138(12):1334-1338.
7. Matthiessen P, Hallbook O, Andersson M, Rutegard J, Sjodahl R. Risk factors for anastomotic leakage after anterior resection of the rectum. Colorectal Dis 2004; 6(6):462-469.
8. Saha AK, Tapping CR, Foley GT, Baker RP, Sagar PM, Burke DA et al. Morbidity and mortality after closure of loop ileostomy. Colorectal Dis 2009; 11(8):866-871.
9. Nastro P, Knowles CH, McGrath A, Heyman B, Porrett TR, Lunniss PJ. Complications of intestinal stomas. Br J Surg 2010; 97(12):1885-1889.
10. den Dulk M, Smit M, Peeters KC, Kranenbarg EM, Rutten HJ, Wiggers T et al. A multivariate analysis of limiting factors for stoma reversal in patients with rectal cancer entered into the total mesorectal excision (TME) trial: a retrospective study. Lancet Oncol 2007; 8(4):297-303.
11. Harris DA, Egbeare D, Jones S, Benjamin H, Woodward A, Foster ME. Complications and mortality following stoma formation. Ann R Coll Surg Engl 2005; 87(6):427-431.
12. Pachler J, Wille-Jorgensen P. Quality of life after rectal resection for cancer, with or without permanent colostomy. Cochrane Database Syst Rev 2004;(3):CD004323.
13. Floodeen H, Lindgren R, Matthiessen P. When are defunctioning stomas in rectal cancer surgery really reversed? Results from a population-based single center experience. Scand J Surg 2013; 102(4):246-250.
14. Dikken JL, Wouters MW, Lemmens VE, Putter H, van der Geest LG, Verheij M et al. Influence of hospital type on outcomes after oesophageal and gastric cancer surgery. Br J Surg 2012; 99(7):954-963.

15. Elferink MA, Wouters MW, Krijnen P, Lemmens VE, Jansen-Landheer ML, van de Velde CJ et al. Disparities in quality of care for colon cancer between hospitals in the Netherlands. Eur J Surg Oncol 2010; 36 Suppl 1:S64-S73.
16. Goossens-Laan CA, Visser O, Wouters MW, Jansen-Landheer ML, Coebergh JW, van de Velde CJ et al. Variations in treatment policies and outcome for bladder cancer in the Netherlands. Eur J Surg Oncol 2010; 36 Suppl 1:S100-S107.
17. van Steenbergen LN, van de Poll-Franse LV, Wouters MW, Jansen-Landheer ML, Coebergh JW, Struikmans H et al. Variation in management of early breast cancer in the Netherlands, 2003-2006. Eur J Surg Oncol 2010; 36 Suppl 1:S36-S43.
18. Wouters MW, Siesling S, Jansen-Landheer ML, Elferink MA, Belderbos J, Coebergh JW et al. Variation in treatment and outcome in patients with non-small cell lung cancer by region, hospital type and volume in the Netherlands. Eur J Surg Oncol 2010; 36 Suppl 1:S83-S92.
19. van der Heiden-van der Loo, de ML, Visser O, Westenend PJ, van DT, Menke MB et al. Variation between hospitals in surgical margins after first breast-conserving surgery in the Netherlands. Breast Cancer Res Treat 2012; 131(2):691-698.
20. Paul-Shaheen P, Clark JD, Williams D. Small area analysis: a review and analysis of the North American literature. J Health Polit Policy Law 1987; 12(4):741-809.
21. McPherson K, Wennberg JE, Hovind OB, Clifford P. Small-area variations in the use of common surgical procedures: an international comparison of New England, England, and Norway. N Engl J Med 1982; 307(21):1310-1314.
22. van der Sanden GA, Coebergh JW, Schouten LJ, Visser O, van Leeuwen FE. Cancer incidence in The Netherlands in 1989 and 1990: first results of the nationwide Netherlands cancer registry. Coordinating Committee for Regional Cancer Registries. Eur J Cancer 1995; 31A(11):1822-1829.
23. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001; 345(9):638-646.
24. Snijders HS, van den Broek CB, Wouters MW, Meershoek-Klein KE, Wiggers T, Rutten H et al. An increasing use of defunctioning stomas after low anterior resection for rectal cancer. Is this the way to go? Eur J Surg Oncol 2013; 39(7):715-720.
25. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 2009; 373(9666):811-820.
26. Chang JS, Keum KC, Kim NK, Baik SH, Min BS, Huh H et al. Preoperative chemoradiotherapy effects on anastomotic leakage after rectal cancer resection: a propensity score matching analysis. Ann Surg 2014; 259(3):516-521.
27. den Dulk M., Smit M, Peeters KC,

Kranenbarg EM, Rutten HJ, Wiggers T et al. A multivariate analysis of limiting factors for stoma reversal in patients with rectal cancer entered into the total mesorectal excision (TME) trial: a retrospective study. Lancet Oncol 2007; 8(4):297-303.
28. Poon RT, Chu KW, Ho JW, Chan CW, Law WL, Wong J. Prospective evaluation of selective defunctioning stoma for low anterior resection with total mesorectal excision. World J Surg 1999; 23(5):463-467.
29. Eriksen MT, Wibe A, Norstein J, Haffner J, Wiig JN. Anastomotic leakage following routine mesorectal excision for rectal cancer in a national cohort of patients. Colorectal Dis 2005; 7(1):51-57.
30. Lefebure B, Tuech JJ, Bridoux V, Costaglioli B, Scotte M, Teniere P et al. Evaluation of selective defunctioning stoma after low anterior resection for rectal cancer. Int J Colorectal Dis 2008; 23(3):283-288.
31. Enker WE, Merchant N, Cohen AM, Lanouette NM, Swallow C, Guillem J et al. Safety and efficacy of low anterior resection for rectal cancer: 681 consecutive cases from a specialty service. Ann Surg 1999; 230(4):544-552.
32. Dekker JW, Liefers GJ, de Mol van Otterloo JC, Putter H, Tollenaar RA. Predicting the risk of anastomotic leakage in left-sided colorectal surgery using a colon leakage score. J Surg Res 2011; 166(1):e27-e34.
33. Messaris E, Sehgal R, Deiling S, Koltun WA, Stewart D, McKenna K et al. Dehydration is the most common indication for readmission after diverting ileostomy creation. Dis Colon Rectum 2012; 55(2):175-180.
34. Chun LJ, Haigh PI, Tam MS, Abbas MA. Defunctioning loop ileostomy for pelvic anastomoses: predictors of morbidity and nonclosure. Dis Colon Rectum 2012; 55(2):167-174.
35. Gastinger I, Marusch F, Steinert R, Wolff S, Koeckerling F, Lippert H. Protective defunctioning stoma in low anterior resection for rectal carcinoma. Br J Surg 2005; 92(9):1137-1142.
36. Pakkastie TE, Ovaska JT, Pekkala ES, Luukkonen PE, Jarvinen HJ. A randomised study of colostomies in low colorectal anastomoses. Eur J Surg 1997; 163(12):929-933.
37. Snijders HS, Bakker IS, Dekker JW, Vermeer TA, Consten EC, Hoff C et al. High 1-year complication rate after anterior resection for rectal cancer. J Gastrointest Surg 2014; 18(4):831-838.
38. Gooszen AW, Geelkerken RH, Hermans J, Lagaay MB, Gooszen HG. Temporary decompression after colorectal surgery: randomized comparison of loop ileostomy and loop colostomy. Br J Surg 1998; 85(1):76-79.