Value of outcomes research in colorectal cancer care

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Chapter 6

REDUCED 30 DAY MORTALITY AFTER LAPAROSCOPIC COLORECTAL CANCER SURGERY: A POPULATION BASED STUDY FROM THE DUTCH SURGICAL COLORECTAL AUDIT (DSCA).

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ABSTRACT

Objective: To evaluate the impact of a laparoscopic resection on postoperative mortality after colorectal cancer surgery.

Summary background data: The question whether laparoscopic resection (LR) compared to open resection (OR) for colorectal cancer influences the risk of postoperative mortality remains unresolved. Several meta-analyses showed a trend, but failed to reach statistical significance. The exclusion of high-risk patients and insufficient power might be responsible for that. We analyzed the influence of LR on postoperative mortality in a risk-stratified comparison and secondly we studied the effect of LR on postoperative morbidity.

Methods: Data from the Dutch Surgical Colorectal Audit (2010 - 2013) was used. Homogenous subgroups of patients were defined based on factors influencing the choice of surgical approach and risk factors for postoperative mortality. Crude mortality rates were compared between LR and OR. The influence of LR on postoperative complications was evaluated using both univariable and multivariable analysis.

Results: In patients undergoing elective surgery for non-locally advanced, non-metastasized colon cancer, LR was associated with a significant lower risk of postoperative mortality compared to OR in 20/22 subgroups. LR was independently associated with a lower risk of cardiac (OR 0.73, 95% CI 0.66-0.82) and respiratory (OR 0.73, 95% CI 0.64-0.84) complications.

Conclusions: LR reduces the risk of postoperative mortality compared to OR in elective setting in patients with non-locally advanced, non-metastasized colorectal cancer. Especially elderly frail patients seem to benefit because of reduced cardiopulmonary complications. These findings support widespread implementation of LR for colorectal cancer, also in patients at high operative risk.

INTRODUCTION

The reduction of surgical trauma by minimally invasive techniques in both colon and rectal cancer surgery has been shown to result in faster postoperative recovery compared to conventional open surgery, without compromising oncological outcome.[1, 2] This has been demonstrated with the highest level of evidence by meta-analyses of randomized controlled trials (RCTs). Long-term benefits of laparoscopic resection for colorectal cancer are better cosmetics, less incisional hernias due to preserved abdominal wall integrity, and less adhesion related small bowel obstruction.[3-5] Considering costs, laparoscopic colorectal surgery seems to be cost-effective because of reduced hospital stay despite higher intra-operative costs, which may become even more pronounced in the long run given the lower rate of readmissions and re-operations for small bowel obstruction and incisional hernia.[5, 6]

A still unresolved question is whether a laparoscopic approach influences the risk of postoperative mortality after colorectal cancer surgery. Several meta-analyses of RCTs showed a trend towards lower postoperative mortality in favor of laparoscopic resection, but failed to reach statistical significance.[1, 7, 8] The inclusion of relatively low risk patients and the lack of sufficient power are probably responsible for that.

Population studies can solve this problem because of higher numbers of patients. In addition, high-risk patients with higher event rates are included in these studies reflecting daily practice.[9-12] Therefore, the purpose of this population-based analysis was to compare postoperative mortality between laparoscopic and open resection of colorectal cancer in homogenous subgroups based on known operative risk factors. By using a risk-stratified comparison, it was intended to minimize the inherent risk of selection bias in population studies. Secondly we studied the effect of laparoscopic surgery on postoperative morbidity, especially cardiopulmonary complications, in order to investigate one of the mechanisms by which laparoscopic resection could lead to lower postoperative mortality.

METHODS

Data were derived from the Dutch Surgical Colorectal Audit (DSCA), a disease specific national audit.[13] This audit collects information on patient, tumor, treatment and 30 day and in-hospital outcome characteristics of all patients undergoing a resection for primary colorectal carcinoma in the Netherlands. The dataset is based on evidence-based guidelines and is cross-checked on a yearly basis with data from the Netherlands Cancer Registry (NCR).[14] All Dutch hospitals participate, with approximately 97 percent completeness in 2012 based on comparison with the NCR. Details of the DSCA regarding data collection and methodology have been published previously.[13, 15]

Patients

For this study, no ethical approval or informed consent was required under Dutch law. All patients (n=37,871) undergoing surgical resection for primary colorectal cancer between January 1st, 2010 and December 31th, 2013, and registered in the DSCA before April 15th, 2014, were evaluated. Minimal data requirements to consider a patient eligible for analysis were information on tumor location, date of surgery and 30-day mortality (n=37,636). For the purpose of this study, patients who underwent transanal resection (n=244) were excluded. Furthermore, the heterogenous group of patients with multiple synchronous colorectal tumors (n=1396) were excluded.[16] One hospital did not have reliable outcomes of postoperative mortality in 2010 and 2011 due to incorrect electronic input of data and corresponding patients were excluded (n=274). One hospital closed during 2011 and the registered 8 patients from that year were also excluded (n=8).

Surgical approach at hospital level

Practice patterns of surgical approach for resection of colorectal cancer in the Netherlands in 2010 based on the DSCA have been published previously.[12] A mean laparoscopic resection rate of 44% at patient level was found, with a laparoscopic resection rate ranging between 0% and 96% at hospital level. In order to be informed about hospital variation in use of laparoscopic resection since then, the proportion of laparoscopic resections for colorectal cancer per hospital per year was calculated, with conversion to open surgery being included in the laparoscopic group. Six hospitals didn't have results for the full study period; two due to hospital closure, three hospitals had incompatible datasets for specific years which could not be implemented in the DSCA database and one due to the earlier mentioned non-plausible outcome on postoperative mortality. Hospitals were categorized into three groups; low- (0-33%), medium- (33-67%) and high- (67-100%) rate laparoscopic resection hospitals, according to the percentage of laparoscopic colorectal cancer resections in these hospitals. Potential differences in baseline characteristics of patient populations between these three categories were assessed in order to be aware of confounding factors determining the surgical approach.

Data analysis and risk stratification

For the purpose of analyzing the primary aim of this study, homogenous subgroups were defined based on potential factors influencing the choice of surgical approach (locally advanced tumor, previous abdominal surgery, elective or emergency setting), and known risk factors for postoperative mortality (elective or emergency setting, age, ASA classification, tumor stage). Analyses were performed separately for colon and rectal cancer. Type of previous abdominal surgery is not specified in the DSCA. This may entail for example laparoscopic appendectomy or prior open bowel resection. For this reason, analyses were performed with and without including patients with previous abdominal surgery. Procedures were defined as an open resection (OR) or a laparoscopic resection (LR) based on the intentional approach of the resection. In this way, converted LR was included in the LR group. Crude mortality rates were compared between OR and LR in the predefined subgroups. This analysis was chosen as an alternative to casemix adjusted comparison between OR and LR in the whole group of patients, because we wanted to determine if the impact of surgical approach differs among groups of patients with different operative risk.

Differences in postoperative mortality rates were analyzed using a chi-square test with a significance level of 0.05. A relative risk of postoperative mortality with 95% confidence interval and corresponding relative risk reduction was calculated for each subgroup. This analysis was repeated for the same subgroups, excluding patients with a converted laparoscopic resection. The influence of laparoscopic resection on different postoperative complications that may contribute to the risk of postoperative mortality were evaluated using both univariable and multivariable analysis. The significance level of univariable analysis was set at a two-tailed p-value of 0.05, but factors were entered in the multivariable analysis at a p-value of less than 0.10 using an ENTER model. The following factors were included in multivariable analysis to adjust for differences in casemix between OR and LR; sex, age, ASA classification, BMI, previous abdominal surgery, emergency surgery, additional resection for locally advanced/metastatic disease, pT-classification, and metastatic disease. No process or treatment characteristics were included in the multivariable analysis for risk-adjustment. Statistical analyses were performed in PASW Statistics, version 20 (SPSS inc., Chicago, IL).

RESULTS

Patients and hospitals

A total of 35,714 patients, registered by 92 hospitals, met the inclusion criteria. Annual laparoscopic resection rates at hospital level were calculated. This showed hospitals still performing laparoscopic resection on an incidental basis, hospitals with laparoscopic resection being already fully implemented at the start of the study period, and in between several stable, increasing or decreasing levels of application of laparoscopic resection. The overall laparoscopic resection rate increased from 37 percent in 2010 to 58 percent in 2013. The percentage of converted laparoscopic resections decreased from 13.6 percent in 2010 to 13.3 percent in 2013. Categorization by the rate of laparoscopic resection per hospital resulted in 29 low-rate laparoscopic resection (LRL) hospitals, 46 medium-rate laparoscopic resection (MRL) and 17 high-rate laparoscopic resection (HRL) hospitals, in which 11,579, 18,191 and 5,944 patients were treated, respectively. Table 1 shows the distribution of casemix factors among LRL, MRL and HRL hospitals. Patient characteristics were similar among the three types of hospitals, but LRL hospitals treated up to 5 percent more patients with locally advanced disease and up to 4.5 percent more patients with metastatic disease compared to MRL and HRL hospitals.

Risk stratified comparison of postoperative mortality

The overall percentage of postoperative mortality for this study period was 3.3 percent; 3.9 percent for patients with colon carcinoma and 2.0 percent for patients with rectal carcinoma.

Emergency surgery, T4 stage and M1 stage were excluded for the purpose of the primary analysis of postoperative mortality after laparoscopic and open approach, based on the observed casemix differences among the three hospital categories and the generally considered relative contraindications for a laparoscopic approach. Within the total group of patients undergoing elective surgery for non-locally advanced, non-metastasized colorectal cancer (T1-3N0-2M0 stage), 22 different subgroups were defined based on age (<70, ≥70 and ≥80 years), ASA score (1-2 and 3-4), and previous abdominal surgery.

Postoperative mortality was lower after LR compared to OR in all 22 subgroups after elective resection of T1-3N0-2M0 colon cancer (Table 2), with an absolute risk reduction ranging from 0.4% (<70 years, ASA 1-2) to 4.6% (≥80 years, ASA 3-4). The lower relative risk of postoperative mortality after LR was statistically significant in 20 of 22 subgroups, with a range between 0.18 (95% confidence interval (CI) 0.05-0.66) and 0.64 (95% CI 0.45-0.90). After elective surgery for T1-3N0-2M0 rectal cancer, postoperative mortality differed significantly in 4 of 22 subgroups. In patients of 70 years and older, with or without previous abdominal surgery, LR resulted in an absolute risk reduction of mortality of 1.8 and 2.4 percent and a relative risk of 0.58 (95% CI 0.41-0.82) and 0.53 (95% CI 0.35-0.81), respectively. The other two subgroups consisted of patients of 70 years and older, and ASA 3-4 with or without previous abdominal surgery: absolute risk reduction of 4.0 and 4.7 percent and relative risk of 0.57 (95% CI 0.35-0.92) and 0.56 (95% CI 0.32-0.98), respectively.

Emergency surgery and advanced disease were analyzed in a secondary analysis with a relatively high risk of bias. Significantly different mortality rates were found for elective colon surgery for T4 stage and emergency colonic surgery, with or without previous abdominal surgery, in favor of LR (Table 2).

The analysis was repeated for all the above-mentioned subgroups excluding patients with a converted laparoscopic resection. This showed nearly equal results, with an equal amount of subgroups in which laparoscopic resection led to a significantly lowered percentage of postoperative mortality (data not shown).

Surgical approach and postoperative complications

Table 3 shows the surgical and non-surgical postoperative complication rates after OR and LR. In univariable analysis, surgical complications and any type of non-surgical complications were significantly higher in the OR group. Multivariable analysis showed an OR of 0.66 (95% CI 0.63 – 0.70) for overall postoperative complications in favor of LR. A laparoscopic approach was also independently associated with a lower risk of surgical complications (OR 0.88; 95% CI 0.83 – 0.94), pulmonary complications (OR 0.73; 95% CI 0.66 – 082), cardiac complications (OR 0.73; 95% CI 0.64 – 0.84), infectious complications (OR 0.74; 95% CI 0.66 – 0.84), and other complications (OR 0.72; 95% CI 0.65 – 0.79).

DISCUSSION

This population-based study demonstrates the significantly reduced risk of postoperative mortality after laparoscopic resection compared to open surgery in patients with non-locally advanced, non-metastatic colon cancer in an elective setting. The relative risk reduction was approximately 50% for all risk categories, but this translated into an absolute lower mortality rate of 0.4 percent in a priori low risk patients (<70 years, ASA 1-2) and 4.6 percent in a priori high risk patients (≥80 years, ASA 3-4). These observations were similar in rectal cancer, but differences in mortality were less often statistically significant due to lower numbers of patients and events. In contrast to what is often believed, our data shows that especially high-risk patients benefit from laparoscopic surgery. The present finding of a significant reduction of non-surgical complications associated with laparoscopic surgery, e.g. cardiopulmonary complications, demonstrates the clinical implications of reduced surgical stress response that becomes most apparent in the elderly frail patients.

The effect of laparoscopic surgery on postoperative mortality has been studied previously. Meta-analyses of RCTs showed a trend towards lower postoperative mortality for laparoscopic resection compared to an open approach. The recently updated Cochrane analysis showed a relative risk of 0.81 in favor of laparoscopic resection, but with a wide confidence interval (95% CI 0.50-1.32).[17] A meta-analysis published in 2012 included 3 RCTs in ERAS setting and showed an OR for postoperative mortality of 0.33 (95% CI 0.09-1.18) in favor of laparoscopic resection.[7] All these meta-analyses, however, lacked sufficient power to demonstrate a significant relationship between laparoscopic surgery and lowered postoperative mortality in the relatively healthy study populations that were included in the individual trials.

Population studies on the subject are able to include higher numbers of patients from daily clinical practice with different operative risk levels, compared to RCTs with strict selection criteria. In 2012, we reported a lower casemix corrected mortality rate after laparoscopic surgery compared to open resection (2.4% versus 4.0%; OR 0.63; P<0.01) based on all patients registered in the DSCA in 2010.[12] Other population studies have confirmed these findings.[9-11] The question remained to what extend the results of these analyses were subject to selection bias and which specific patient groups would benefit most from a minimally invasive approach. While casemix correction reduces the effect of confounding factors, it is not likely that a multivariable model in a heterogeneous population will sufficiently correct for the whole range of factors that may influence the decision to perform open or laparoscopic surgery. To deal with these inherent methodological problems of non-randomized comparisons in a different way, we tried to gain more insight by using a risk-stratified comparison between relatively homogenous subgroups. Analysis of the laparoscopic resection rate at hospital level revealed that selection bias was most likely related to advanced disease while the other casemix factors were remarkably comparable among the low, medium and high laparoscopy hospitals. Apparently, low and high laparoscopy hospitals are treating similar patients, except for a small subgroup. This led us to conclude that the decision on the surgical approach in non-metastatic localized colorectal cancer seems to be hospital driven, depending on the availability of adequate equipment and surgeons experienced in the technique. Based on this conclusion, one may also hypothesize that better results after a laparoscopic approach are not only explained by the technique itself, but also by the quality of the surgeons and hospital setting. However, it is difficult to prove that laparoscopy is performed by 'better' surgeons in 'better' hospitals.

Although a RCT is considered to provide the highest level of evidence, its restrictions become more and more apparent. National health registries are a unique source of data, due to the absence of preselected populations and large numbers of patients. In this way, research questions that are unlikely to be answered in RCTs can be analyzed with high external validity because it reflects daily clinical practice. The comparison between laparoscopic and open surgery for colorectal carcinoma is a good example of its usage.

The largest reduction in absolute mortality rate by the use of laparoscopic surgery was found in subgroups comprising high-risk patients. The reduction of the surgical stress response caused by laparoscopic surgery could, theoretically speaking, lead to the reduction of postoperative complications. A pooled analysis of 11 studies, analyzing the use of laparoscopic resection in an elderly population, showed a significant difference in pulmonary and cardiac complications.[18] Elderly patients who underwent open surgery showed a doubled rate of cardiopulmonary complications compared to patients of similar age who underwent laparoscopic resection. Initially, elderly patients with increased cardiopulmonary risk were considered a contraindication for a laparoscopic approach, because of high intra-abdominal pressure and extreme Trendelenburg positioning during laparoscopic surgery with negative impact on ventilation and hemodynamics related to reduced venous return.[19] However, the postoperative risk of open surgery with a higher stress response and pain might be more likely to influence the outcome rather than the intra-operative risk which can often be adequately managed during anesthesia. Support for this mechanism is found in the Dutch LAFA study which describes the inflammatory response in four study arms; laparoscopic or open resection with or without ERAS perioperative care.[20] Human Leukocyte Antigen (HLA-DR) expression, indicating immune competence, showed the highest levels in patients undergoing a laparoscopic resection with ERAS care. Interleukin 6 (IL-6), indicating inflammatory response, showed the highest levels in patients undergoing an open procedure without ERAS.[21] Wang et al. confirmed this finding in 2012.[22] The relationship between the systemic inflammatory response after surgery and the prognosis of the patient has been widely studied in oncologic surgery. The validated Glasgow prognostic score, consisting of preoperative CRP and albumin has an independently predicting value for cancer specific survival.[23, 24] In the light of the lowered postoperative inflammatory response caused by laparoscopic surgery, minimal invasive surgery could be of positive effect on cancer specific survival as well, although long-term results of RCTs do not support this.

Limitations of the present population bases analysis are the methodological issues related to a non-randomized comparison with risk of selection bias, as already mentioned. Differences in postoperative care among the hospitals may have contributed to the present findings, although recent meta-analyses showed that ERAS has no impact on postoperative mortality and that laparoscopy has independent advantages beyond ERAS care.[25, 26] Furthermore, the DSCA only provides 30-day and in-hospital mortality rates, while 90-day or even 1-year mortality rates may be more appropriate, especially in the elderly frail patients. In the near future, we plan to match the two databases of the DSCA and national cancer registry at an individual patient level, which enables similar analyses on long-term outcome.

In conclusion, this population-based analysis demonstrates a reduced mortality risk after elective minimally invasive surgery for localized colorectal cancer compared to an open approach, especially in a priori high-risk patients. The implication of these findings are further implementation of laparoscopic colorectal surgery by facilitating adequate training of colorectal surgeons and providing an adequate infrastructure in hospitals and countries in which open surgery is still standard of care.

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TABLES

Table 1: Baseline characteristics of low- (LRL), medium- (MRL) and high-rate laparoscopy (HRL) hospitals. ASA; American Society of Anesthesiologist classification, BMI; Body Mass Index, M1; Metastatic disease

	Colon				**Rectum**			
	Laparoscopic Rate				**Laparoscopic Rate**			
	LRL	**MRL**	**HRL**	**$\chi 2$**	**LRL**	**MRL**	**HRL**	**$\chi 2$**
Patient								
Male	52%	52%	53%	0.559	63%	62%	62%	0.667
Age 70+	58%	58%	57%	0.714	43%	45%	43%	0.047
ASA III+	25%	27%	26%	0.027	16%	18%	15%	0.001
BMI 30+	15%	15%	14%	0.212	15%	15%	14%	0.859
Previous abdominal surgery	35%	35%	35%	0.898	32%	31%	28%	0.010
Tumor								
Pathological T4	19%	17%	14%	<0.001	6.6%	3.7%	3.5%	<0.001
M1	15%	12%	12%	<0.001	10%	6.1%	5.5%	<0.001
Surgery								
Non-elective surgery	20%	20%	19%	0.313	1.7%	1.7%	1.4%	0.590
Additional resection				0.002				<0.001
due to tumor invasion, extensive	5.3%	4.4%	3.8%		6.9%	2.1%	2.9%	
due to tumor invasion, limited	6.0%	6.4%	6.8%		3.6%	3.2%	4.0%	
Additional resection due to metastasis	5.2%	3.0%	3.3%	<0.001	5.3%	1.8%	2.1%	<0.001

Table 2a: Percentage of postoperative mortality for open and laparoscopic surgery in different subgroups of patients stratified by perioperative risk. ARR; absolute risk reduction, RR; relative risk, RRR; relative risk reduction, ASA; American Society of Anesthesiologist classification, T4; pathological T4, M1; metastatic disease.

Risk group	Mortality N (%) Open	Mortality N (%) Laparoscopy	ARR %	RR (95% CI)	RRR %	P-value
Colon cancer, elective, T1-3N0-2M0						
<70	26/2436 **(1.1)**	18/4120 **(0.4)**	0.7	0.41 (0.22-0.74)	59	0.003
>70	238/4481 **(5.3)**	152/5137 **(3.0)**	2.3	0.54 (0.44-0.67)	46	<0.001
>80	160/1950 **(8.2)**	91/1900 **(4.8)**	3.4	0.56 (0.43-0.73)	44	<0.001
ASA 1-2	98/5005 **(2.0)**	75/7325 **(1.0)**	1.0	0.52 (0.38-0.70)	48	<0.001
ASA 3-4	166/1893 **(8.8)**	96/1924 **(5.0)**	3.8	0.55 (0.42-0.71)	45	<0.001
<70, ASA 1-2	14/2107 **(0.7)**	11/3670 **(0.3)**	0.4	0.45 (0.20-0.99)	55	0.042
>70, ASA 1-2	84/2898 **(2.9)**	64/3655 **(1.8)**	1.1	0.60 (0.43-0.83)	40	0.002
>80, ASA 1-2	59/1098 **(5.4)**	38/1170 **(3.2)**	2.2	0.59 (0.39-0.90)	41	0.012
<70, ASA 3-4	12/319 **(3.8)**	7/445 **(1.6)**	2.2	0.41 (0.16-1.05)	59	0.055
>70, ASA 3-4	154/1574 **(9.8)**	88/1478 **(6.0)**	3.8	0.58 (0.45-0.77)	42	<0.001
>80, ASA 3-4	101/851 **(11.9)**	53/728 **(7.3)**	4.6	0.58 (0.41-0.83)	42	0.002
Rectal cancer, elective, T1-3N0-2M0						
<70	12/2228 **(0.5)**	15/2694 **(0.6)**	-0.1	1.03 (0.48-2.21)	-3	0.931
>70	80/1823 **(4.4)**	53/2050 **(2.6)**	1.8	0.58 (0.41-0.82)	42	0.002
>80	33/562 **(5.9)**	28/601 **(4.7)**	1.2	0.78 (0.47-1.31)	22	0.354

Continuation of Table 2a

ASA 1-2	40/3306 **(1.2)**	35/4050 **(0.9)**	0.3	0.71 (0.45-1.12)	29	0.142
ASA 3-4	51/732 **(7.0)**	33/690 **(4.8)**	2.2	0.67 (0.43-1.05)	33	0.810
<70, ASA 1-2	9/1988 **(0.5)**	11/2497 **(0.4)**	0.1	0.97 (0.40-2.35)	3	0.951
>70, ASA 1-2	31/1318 **(2.4)**	24/1553 **(1.5)**	0.9	0.65 (0.38-1.12)	35	0.116
>80, ASA 1-2	15/354 **(4.2)**	14/396 **(3.5)**	0.7	0.83 (0.39-1.74)	17	0.619
<70, ASA 3-4	2/236 **(0.8)**	4/196 **(2.0)**	-1.2	2.49 (0.44-13.45)	-149	0.291
>70, ASA 3-4	49/496 **(9.9)**	29/494 **(5.9)**	4.0	0.57 (0.35-0.92)	43	0.019
>80, ASA 3-4	18/206 **(8.7)**	14/205 **(6.8)**	1.9	0.77 (0.37-1.58)	23	0.470
Colorectal cancer, advanced disease, non-elective surgery						
Colon, elective, T4	79/1745 **(4.5)**	21/1027 **(2.0)**	2.5	0.44 (0.27-0.72)	56	0.001
Colon, Elective, M1	53/1352 **(3.9)**	22/767 **(2.9)**	1.0	0.72 (0.44-1.20)	28	0.208
Colon, emergency	362/4379 **(8.3)**	28/648 **(4.3)**	4.0	0.50 (0.34-0.74)	50	<0.001
Rectum, elective, T4	7/319 **(2.2)**	5/122 **(4.1)**	-1.9	1.91 (0.59-6.12)	-91	0.272
Rectum, elective, M1	6/459 **(1.3)**	3/228 **(1.3)**	0.0	1.01 (0.25-4.06)	-1	0.993
Rectum, emergency	17/119 **(14.3)**	2/46 **(4.3)**	10.0	0.27 (0.06-1.23)	73	0.073

Table 2b: Percentage of postoperative mortality for open and laparoscopic surgery in different subgroups of patients, excluding patients with previous abdominal surgery, stratified by perioperative risk. ARR; absolute risk reduction, RR; relative risk, RRR; relative risk reduction, ASA; American Society of Anesthesiologist classification, T4; pathological T4, M1; metastatic disease.

Risk group	Mortality N (%) Open	Mortality N (%) Laparoscopy	ARR %	RR (95% CI)	RRR %	P-value
Colon cancer, elective, T1-3N0-2M0						
<70	22/1569 **(1.4)**	10/2996 **(0.3)**	1.1	0.24 (0.11-0.51)	76	<0.001
>70	130/2430 **(5.3)**	99/3225 **(3.1)**	2.2	0.56 (0.43-0.73)	44	<0.001
>80	86/1011 **(8.5)**	58/1139 **(5.1)**	3.4	0.58 (0.41-0.81)	42	0.002
ASA 1-2	58/2986 **(1.9)**	45/4990 **(0.9)**	1.0	0.46 (0.31-0.68)	54	<0.001
ASA 3-4	94/1022 **(9.2)**	64/1225 **(5.2)**	4.0	0.54 (0.39-0.76)	46	<0.001
<70, ASA 1-2	12/1383 **(0.9)**	7/2674 **(0.3)**	0.6	0.30 (0.12-0.76)	70	0.007
>70, ASA 1-2	46/1603 **(2.9)**	38/2316 **(1.6)**	1.3	0.57 (0.37-0.87)	43	0.009
>80, ASA 1-2	33/574 **(5.7)**	22/712 **(3.1)**	2.6	0.52 (0.30-0.91)	48	0.019
<70, ASA 3-4	10/199 **(5.0)**	3/319 **(0.9)**	4.1	0.18 (0.05-0.66)	82	0.004
>70, ASA 3-4	84/823 **(10.2)**	61/906 **(6.7)**	3.5	0.64 (0.45-0.90)	36	0.009
>80, ASA 3-4	53/437 **(12.1)**	36/425 **(8.5)**	3.6	0.67 (0.43-1.05)	33	0.078

Continuation of Table 2b

Rectal cancer, elective, T1-3N0-2M0						
<70	7/1616 **(0.4)**	11/2068 **(0.5)**	-0.1	1.23 (0.48-3.18)	-77	0.670
>70	57/1103 **(5.2)**	39/1380 **(2.8)**	2.4	0.53 (0.35-0.81)	47	0.003
>80	23/312 **(7.4)**	20/383 **(5.2)**	2.2	0.69 (0.37-1.29)	31	0.242
ASA 1-2	26/2244 **(1.2)**	24/2974 **(0.8)**	0.4	0.69 (0.39-1.21)	31	0.197
ASA 3-4	37/466 **(7.9)**	26/472 **(5.5)**	2.4	0.68 (0.40-1.14)	32	0.137
<70, ASA 1-2	4/1447 **(0.3)**	8/1929 **(0.4)**	-0.1	1.50 (0.45-5.00)	-50	0.504
>70, ASA 1-2	22/797 **(2.8)**	16/1045 **(1.5)**	1.3	0.55 (0.29-1.05)	45	0.066
>80, ASA 1-2	10/188 **(5.3)**	9/248 **(3.6)**	1.7	0.67 (0.27-1.68)	33	0.392
<70, ASA 3-4	2/165 **(1.2)**	3/138 **(2.2)**	-1.0	1.81 (0.30-11.00)	-81	0.513
>70, ASA 3-4	35/301 **(11.6)**	23/334 **(6.9)**	4.7	0.56 (0.32-0.98)	44	0.038
>80, ASA 3-4	13/122 **(10.7)**	11/135 **(8.1)**	2.6	0.74 (0.32-1.73)	26	0.490
Colorectal cancer, advanced disease, non-elective surgery						
Colon, elective, T4	39/1084 **(3.6)**	13/713 **(1.8)**	1.8	0.50 (0.26-0.94)	50	0.028
Colon, elective, M1	24/852 **(2.8)**	16/541 **(3.0)**	-0.2	1.05 (0.55-2.00)	-5	0.878
Colon, emergency	250/3001 **(8.3)**	20/474 **(4.2)**	4.1	0.49 (0.30-0.77)	51	0.002
Rectum, elective, T4	4/175 **(2.3)**	4/94 **(4.3)**	-2.0	1.90 (0.46-7.78)	-90	0.365
Rectum, elective, M1	3/262 **(1.1)**	2/157 **(1.3)**	-0.2	1.11 (0.18-6.74)	-11	0.906
Rectum, emergency	13/80 **(16.2)**	1/30 **(3.3)**	12.9	0.18 (0.02-1.42)	82	0.070

Table 3: Postoperative complications after OR and LR for colorectal cancer. The following factors were included in the multivariable model to correct for differences in casemix between the two surgical approaches; sex, age, ASA classification, BMI, previous abdominal surgery, emergency surgery, additional resection for locally advanced/metastatic disease, pT-classification, metastatic disease.

	Complication n (%)	**Complication n (%)**	**Odds ratio (CI)**	
Complication type	**Open (n=18861)**	**Laparoscopy (n=16705)**	**Univariable**	**Multivariable**
Postoperative complications	7033 **(37)**	4389 **(26)**	0.60 (0.57-0.63)	0.66 (0.63-0.70)
Surgical complication	3082 **(16)**	2309 **(14)**	0.82 (0.78-0.87)	0.88 (0.83-0.94)
General complication				
Pulmonary	1196 **(6.3)**	660 **(4.0)**	0.61 (0.55-0.67)	0.73 (0.66-0.82)
Cardiac	751 **(4.0)**	404 **(2.4)**	0.60 (0.53-0.68)	0.73 (0.64-0.84)
Thromboembolic	142 **(0.8)**	86 **(0.5)**	0.68 (0.52-0.89)	0.85 (0.63-1.13)
Infectious	838 **(4.4**)	476 **(2.8)**	0.63 (0.56-0.71)	0.74 (0.66-0.84)
Neurologic	267 **(1.4)**	179 **(1.1)**	0.75 (0.62-0.91)	0.94 (0.77-1.16)
Other	1446 **(7.7)**	842 **(5.0)**	0.64 (0.59-0.70)	0.70 (0.63-0.76)