Postoperative Complications Following Surgery for Rectal Cancer

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Objective: This systematic review was designed to determine postoperative complication rates of radical surgery for rectal cancer (abdominal perineal resection and anterior resection).

Summary of Background Data: Lack of accepted complication rates for rectal cancer surgery may hinder quality improvement efforts and may impede the conception of future studies because of uncertainty regarding the expected event rates.

Methods: All prospective studies of rectal cancer receiving radical surgery published between 1990 and August 2008 were obtained by searching Ovid MEDLINE, EMBASE, as well as ASCO GI, CAGS, and ASCRS meeting abstracts between 2004 and 2008. There was no language restriction. The outcomes extracted were anastomotic leak, pelvic sepsis, postoperative death, wound infection, and fecal incontinence. Summary complication rates were obtained using a random effects model; the Z-test was used to test for study heterogeneity.

Results: Fifty-three prospective cohort studies and 45 randomized controlled studies with 36,315 patients (24,845 patients had an anastomosis) were eligible for inclusion. Most of the studies found were based in continental Europe (58%), followed by Asia (25%), United Kingdom (10%), North America (5%), and Australia/New Zealand. The anastomotic leak rate, reported in 84 studies, was 11% (95% CI: 10, 12); the pelvic sepsis rate, in 29 studies, was 12% (9, 16); the postoperative death rate, in 75 studies, was 2% (2, 3); and the wound infection rate, in 50 studies, was 7% (5, 8). Fecal incontinence rates were reported in too few studies and so heterogeneously that numerical summarization was inappropriate. Year of publication, use of preoperative radiation, use of laparoscopy, and use of protecting stoma were not significant variables, but average age, median tumor height, and method of detection (clinical vs. radiologic) showed significance to explain heterogeneity in anastomotic leak rates. Year of publication, study origin, average age, and use of laparoscopy were significant, but median tumor height and preoperative radiation use were not significant in explaining heterogeneity among observed postoperative death rates. With multivariable analysis, only average age for anastomotic leak and year of publication for postoperative death remained significant.

Conclusions: Benchmark complication rates for radical rectal cancer surgery were obtained for use in sample size calculations in future studies and for quality control purposes. Postoperative death rates showed improvement in recent years.

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Rectal cancer is a significant source of morbidity and mortality with 6363 new cases diagnosed in 2005 in Canada[1] and 40,470 estimated new cases diagnosed in 2008 in the United States.[2] The mainstay of treatment for rectal cancer is surgical excision of the affected segment of bowel together with appropriate tumor-specific mesorectal excision. For more advanced rectal cancers, adjuvant therapies in the form of chemotherapy or radiation may be used.[3] Even in cases that are not amenable for cure, surgical excision may still have a role in the palliation of rectal cancer.[4]

Patients undergoing resection for rectal cancer face a number of possible complications and the risk of perioperative mortality.[5] Infectious complications consist of wound infections, intra-abdominal abscesses, and/or anastomotic leaks. Anastomotic leak leads to considerable morbidity and possible mortality, and there is a wide range of reported rates in the literature.[6] Beyond the immediate postoperative risks, patients also risk functional derangements[7] or, even, incontinence,[8] especially after preoperative radiation. Sexual and bladder function may also be adversely affected, probably because of injury to autonomic nerves.[9] Aside from some narrative reviews, there is no systematic review of the postoperative complication rates of rectal cancer surgery in the literature.

These complications lead to significant morbidity for the patients involved and need to be the focus of quality improvement efforts. The lack of universally accepted benchmark complication rates for rectal cancer surgery may hamper self-assessment and improvement efforts of both surgeons and institutions; institutions with worse outcomes than average need to become aware of the problem to be able to make improvements. In addition, complication rates for rectal cancer surgery need to be known in the design of research studies aimed at improving patient outcomes, that is, for sample size calculations.

The aim of this systematic review was to summarize the reported complication rates of anterior resection and abdominoperineal resection (APR) for rectal cancer from prospective studies. We were also interested in examining the effects of several covariables on the reported complication rates.

METHODS

Inclusion/Exclusion Criteria

All prospective studies that described the postoperative course of patients that underwent major surgical excision of adenocarcinoma of the rectum with or without primary anastomosis, that have been published since 1990 were eligible to be included in this systematic review. The studies needed to have at least 50 patients that fulfilled the inclusion or exclusion criteria, and all the patients needed to be more than 18 years of age; both open and laparoscopic surgeries were acceptable.

The studies were excluded if they described the outcomes of local excision, excision involving intersphincteric dissection or surgery for recurrent cancer. Studies that had patients with inflammatory bowel disease or other cancers (ie, carcinoid, sarcoma, melanoma, etc) were also excluded. Studies with a case mix of acceptable and unacceptable cases were included as long as the outcomes of the acceptable group of cases were described separately or the acceptable cases comprised more than 80% of the total.

Randomized controlled trials (RCTs) and prospective cohort studies were the study designs acceptable for this review. RCTs were clearly identified as such from their description of the randomization procedure. The data from RCTs were collapsed into a single cohort, unless the randomization variables was one of the covari-

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ables of this review, in which case the data from the different RCT cohorts were kept separate. Prospective cohort studies were identified by several indicators that showed there had been forethought in the design and implementation of the study; a research question or hypothesis, a sample size calculation, participant consent, a protocol for the conduct of the study were some of the factors that indicated a prospectively conducted study. However, if the study only mentioned that the data were gathered prospectively without any mention of forethought as to the goal of the research, it was considered to be a prospective case series instead of a true prospective cohort study.

Search Strategy and Study Selection

Ovid MEDLINE was searched using the MeSH terms rectum/su, rectal neoplasms/su, postoperative complications, wound infection, anastomosis, surgical and fecal incontinence and the keywords anterior resection, wound infection, anastomotic leak, and fecal incontinence. Similarly, EMBASE was searched using, in addition, the MeSH terms rectum anastomosis, rectum anterior resection, rectum cancer/su, rectum carcinoma/su, rectum resection, rectum surgery, anastomosis leakage, and anastomosis dehiscence. The searches were limited to adult (18+ years old) humans and to the period between 1990 and August 2008. The American Society of Clinical Oncology Gastrointestinal Cancers Symposium, the Canadian Association of General Surgeons, and the American Society of Colon and Rectal Surgeons meeting abstracts for the years 2004–2008 were hand searched for relevant abstracts. The references of the included studies were also searched for any missed studies.

A RefWorks database (available at: www.refworks.com) was used to organize and select the studies. One reviewer (B.P.) eliminated duplicates, and then selected titles for relevancy. The abstracts of the selected titles were read, and the studies further selected for full text review. The title and abstract selection strategy was permissive, such that a study was included if it had any indication of being eligible. The articles selected for full text review were distributed to 2 reviewers (S.C. and B.P.), who independently decided on inclusion/exclusion and independently abstracted the study data; Cohen's kappa coefficient was calculated as a measure of agreement. Any disagreement was resolved by consensus to obtain the final list of eligible studies.

Outcomes and Covariables

The outcomes of interest were rates of abdominal wound infection, anastomotic leak, pelvic sepsis, postoperative death, and fecal incontinence. Pelvic sepsis was defined as either anastomotic leak or pelvic abscess to take into account those studies in which a distinction was not made between leaks and abscesses. Pelvic sepsis was calculated for the studies that reported anastomotic leak and pelvic abscess separately by adding both the incidence. Postoperative death was defined as death from any cause that occurred postoperatively. The reported complications were accepted at face value without trying to reconcile minor differences in the internal definitions of the studies. The complication rates were calculated as crude rates by dividing the observed number of complications by the total number of patients in the cohort for wound infection and postoperative death and by the number of patients that received an anastomosis for anastomotic leak and pelvic sepsis; it was necessary to use the number of patients with an anastomosis, rather than the total number of patients in the cohort, as the denominator for the pelvic sepsis rate so that the resulting pelvic sepsis rate would be larger than the respective anastomotic leak rate. The eligible patients for assessment of fecal incontinence were those that received an anastomosis.

The study variables that were collected were year of publication and geographical area of origin. The origin of the study was the place where the study was designed and most of the patients were accrued and was categorized a priori into North America, Australia/New Zealand, Asia, (continental) Europe, and United Kingdom. The variables describing the cohort of patients that were collected were age (mean), sex (percent male), cohort TNM distribution, and height of the tumor from anal verge (median, in centimeters). The treatment variables that were collected were use of preoperative radiation, use of postoperative radiation, use of laparoscopy, use of perioperative antibiotics, use of protecting stoma (only for patients receiving an anastomosis), proportion of patients given an anastomosis, and method of detection of an anastomotic leak. Preoperative radiation was considered short course if it consisted of 20 to 30 Gy delivered over 5 to 7 days followed within 7 to 10 days by surgery, whereas it was considered long course if it consisted of at least 40 Gy delivered over 6 weeks followed by surgery after at least 5 weeks wait. The method of detection of an anastomotic leak was considered to be clinical if the diagnosis was made after development of symptoms, whereas it was considered to be radiologic if the diagnosis was made after routine radiology tests in all eligible patients. The studies using radiologic detection of anastomotic leaks typically used a water-soluble contrast enema in all patients that received an anastomosis within 7 to 10 days postoperatively if they did not have a protecting stoma or before stoma closure in the patients with a protecting stoma. The follow-up length was recorded for the outcomes of wound infection, anastomotic leak, pelvic sepsis, and postoperative death. From the studies describing the rates of fecal incontinence we collected the main outcome variable and the follow-up period.

Data Abstraction

A data abstraction form was developed, pilot tested on 20 random studies, and modified by agreement between the 2 data abstractors (S.C. and B.P.). On the basis of the paper form, an electronic database was developed in SPSS (version 15.0 for Windows, SPSS Inc, Chicago, IL) and used independently by the 2 abstractors to record the data from all of the included studies. The 2 databases were then compared and any disagreements were reconciled.

Statistical Analysis

The complication rates for each of the outcomes were calculated in Review Manager 4.2 (The Cochrane Collaboration, Oxford, United Kingdom) using a random effects model.[10] The complication rates for each of the studies, which are proportions ($P = y/n$), were transformed using the natural logarithm and the variances of ln(p) were calculated using the delta method[11] by the following equation $\mathrm{Var}(\ln(p)) = (1 - p)/np$. The logarithmic transformation was employed so that the lower bounds of the confidence intervals would not be negative in value. The values of ln(p) and SE(ln(p)) were entered in RevMan as generic inverse variance data type to obtain the complication rates and their 95% confidence intervals. The I^2 statistic was used to represent between study heterogeneity for each of the pooled results.[12]

To test the effects of the covariables on the complication rates, the continuous covariables were dichotomized using their median values. For example, the median year of publication was 2002, so the studies were separated into those that were published between 1990 and 2002 and those that were published between 2003 and 2008. Similarly, the cut-off value for age was 65 years; for height from anal verge, was 6.75 cm; and for preoperative radiation use and for protecting stoma use, was 50% of the cohort. The subgroup complication rates were calculated using RevMan and the differences tested, for dichotomous variables, using a 2-sided z test[13] with $P < 0.05$ considered to be statistically significant. For categorical covariables, like origin of study and preoperative radiation use, pairwise comparisons were made using the z-test as well, but the acceptable *P* value for statistical significance was adjusted by the Bonferroni method (0.05/number of pairwise comparisons). The covariables were dichotomized and the z-test was used because it allowed use of the data obtained from the random effects model. Multivariable analysis using linear regression was used to test the significance of the covariables, used as continuous data where applicable, when combined in a single model.

RESULTS

The study selection process is illustrated in Figure 1. A total of 45 RCTs (Table 1) and 53 prospective cohort studies (Table 2) were deemed eligible for this review; 45 studies were classified as case series and were used for sensitivity analysis. Two of the studies were only available in abstract form,[51,56] whereas some of the studies were available only in foreign languages: Italian,[61] German,[28,29,97] French,[87] and Czech.[93] The agreement for study selection between the 2 reviewers was moderate ($\kappa = 0.55$), with most of the disagreement occurring while trying to differentiate between case series and retrospective studies.

The studies that were included in this review had a total of 36,315 patients, of which 24,845 (68%) were given an anastomosis. Most of the studies originated in continental Europe (58%), followed by Asia (25%), United Kingdom (10%), North America (5%), and Australia/New Zealand (2%).

Complication Rates

The complication rates were not uniformly reported in all of the studies: wound infection reported in 50 studies (51%), anastomotic leak in 84 studies (86%), pelvic sepsis in 29 studies (30%), and postoperative death in 75 studies (77%). The aggregate wound infection rate was 7% (95% CI: 5,8), the anastomotic leak rate was 11%,[10,12] the pelvic sepsis rate was 12%,[9,16] and the postoperative death rate was 2%[2,3] (Table 3). The confidence intervals for wound infection and pelvic sepsis were wider than those for anastomotic

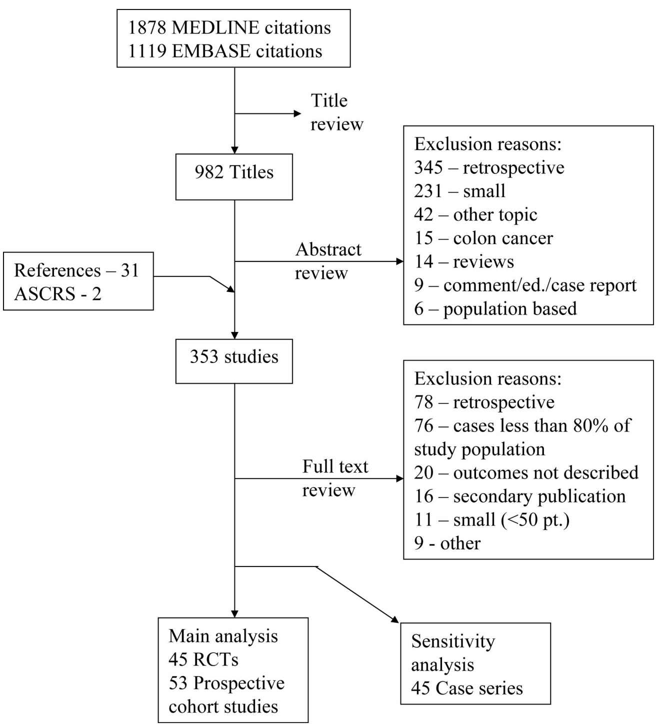

FIGURE 1. Study selection process.

leak rate and postoperative death rate, reflecting the smaller number of studies available. The I^2 statistic was uniformly large for all of the complication rates reflecting both wide variations in the point estimates of individual studies and tight confidence intervals for some of the individual studies. The values of the complication rates obtained from case series were generally lower, but were not significantly different from the findings of the main analysis (results not shown); when the case series were included in the analysis, it did not result in an appreciable change of the findings (Table 3). The actual follow-up length was never reported for the complication rates in the included studies, rather the follow-up was defined in the methods section of some of the studies: 41% of the studies for postoperative death and 16% of the studies for the infectious complications. The postoperative death was defined as any death within 30 days postoperatively in 29 studies, within 60 days in 3 studies, and within the hospital stay in 8 of the studies; there was no significant difference in the postoperative death rate between the groups (results not shown).

The functional outcome, in terms of fecal continence, was poorly reported (Table 4). Only 12 prospective studies could be found that reported on fecal incontinence at all. The studies that were found used a wide variety of scoring systems that were not intuitively understandable or compatible. There was some variation in the length of follow-up, although all of the studies reported after at least a year of follow-up. There was also extreme variation in the reported adverse outcome rates: Fazio et al[52] reported fecal incontinence severity index scores of 31 to 40 and a 63% rate of pad requirement, whereas Park et al[45] reported fecal incontinence severity index scores of 19 to 28 and Heah et al[38] reported a 3% rate of pad requirement. Because of these factors, the fecal incontinence data could not be numerically summarized.

Covariable Effects

Most of the studies included reported on the age (93%), sex (90%), and use of laparoscopy (100%) in their respective cohorts, but many of the other covariables that we were interested in were not reported well: tumor height from anal verge (63%), TNM staging (67%), radiation treatment (62%), protective stoma use (55%), and perioperative antibiotics use (24%). Furthermore, most of the studies reporting perioperative antibiotics use mentioned, in the methods section, that they were routinely given, without a documentation of the actual antibiotics administration. This was deemed highly unreliable so this covariable was eliminated from further analysis.

The median value of the reported average age was 65 years ranging from 44 to 72. There were 3 RCTs and 16 prospective cohort studies that included patients treated with laparoscopy assisted surgery, the rest of the studies had patients treated with conventional, open surgery. The median value of the proportion of stage III disease was 34% ranging from 13 to 77, while the median for stage IV disease was 7% ranging from 0 to 26. The height from anal verge had a median of 6.75 cm ranging from 3 to 10.

The effects of the covariables were only tested on the outcomes of anastomotic leak and postoperative death, because these outcomes have greater importance, while being most commonly reported; in addition, this would reduce the number of comparisons made. The missing covariable data and the small number of studies reporting on wound infection and pelvic sepsis would have severely impaired analysis with respect to these outcomes.

The results of the subgroup analysis on the anastomotic leak and postoperative death are shown in Table 5. The average age, average height, and the method used to detect anastomotic leaks are significant variables that explain some of the heterogeneity in the observed anastomotic leak rates. However, year of publication, study origin, preoperative radiation use, use of laparoscopy, and protecting stoma use do not seem to be significant predictors of the

TABLE 1. Randomized Controlled Studies Describing the Postoperative Complications of Surgical Removal of the Rectum to Treat Cancer

Study	Origin	Study Cohorts	Age	Sex	Height (cm)	Radiation: Short Preop	Radiation: Long Preop	Radiation: Postop	Laparoscopy	Stoma	Patients	Anastomosis	WI Rate	Leak Rate	Pelvic Sepsis Rate	Death Rate
Pahlman and Glimelius[14]	Europe	Preop radiation (short)	72	57	—	100	0	0	No	—	236	33	2	18	22	3
		Postop radiation	70	59	—	0	0	49	No	—	235	34	2	16	22	4
Rowe-Jones et al[15]	United Kingdom	Periop antibiotics	—	—	—	—	—	—	No	—	261	58	10	—	—	—
Dahl et al[16]	Europe	Surgery alone	68	58	7.8	0	0	—	No	—	141	37	3	6	—	2
		Preop radiation (long)	66	58	7.3	0	100	—	No	—	144	36	6	12	—	4
Kwok et al[17]	Asia	Periop antibiotics	61	50	—	—	—	—	No	—	81	49	16	—	10	—
Swedish RCT[18]	Europe	Preop radiation (short)	69	—	—	100	0	—	No	—	572	42	4	11	—	4
		Surgery only	67	—	—	0	0	—	No	—	574	40	5	7	—	3
Sarker et al[19]	Asia	Stapled vs. sewn	60	82	9.9	—	—	—	No	—	60	100	15	15*	—	—
Burke et al[20]	United Kingdom	Bowel preparation	66	57	7.5	—	—	—	No	0	75	100	—	9	—	1
Goldberg et al[21]	United Kingdom	Preop radiation (short)	67	58	—	90	0	—	No	0	228	54	—	15	—	12
		Surgery alone	67	58	—	0	0	—	No	0	239	49	—	13	—	7
Fingerhut et al[22]	Europe	Pelvic drain	64	61	—	—	—	—	No	0	165	0	—	—	—	4
Cedermark et al[23]	Europe	Preop radiation (short)	69	60	—	100	0	—	No	—	424	36	14	7	—	8
		Surgery only	67	57	—	0	0	—	No	—	425	36	9	10	—	2
Stockholm[24]	Europe	Preop radiation (short)	66	61	—	100	0	0	No	—	272	41	15	11	—	2
		Surgery only	66	61	—	0	0	—	No	—	285	41	6	7	—	1
Halbook et al[25]	Europe	Colonic J-pouch	68	54	7	22	0	7	No	65	97	100	8	9	—	1
Medical Research Council[26]	United Kingdom	Surgery only	65	69	7	0	0	—	No	47	140	27	13	26	—	7
		Preop radiation (long)	65	68	7	0	96	—	No	47	139	27	6	24	—	4
Hyams et al[27]	North America	Preop radiation (long)	61	69	—	0	100	0	No	19	32	47	3	20	—	3
		Postop radiation	62	74	—	0	0	100	No	13	39	28	3	18	—	0
Petersen et al[28]	Europe	Surgery only	67	54	—	0	0	—	No	—	46	37	—	29	—	4
		Preop radiation (short)	65	49	—	100	0	—	No	—	47	55	—	15	—	6
Herrman et al[29]	Europe	Surgery only	66	52	—	51	0	35	No	—	93	46	—	21	—	—
Francois et al[30]	Europe	Time radiation to surgery	65	60	5.7	0	100	0	No	40	201	72	—	—	17	3
Tocchi et al[31]	Europe	Omentoplasty	65	56	10.4	—	—	—	No	0	112	100	—	18*	—	—
Brown et al[32]	Asia	Pelvic drain	65	61	4.5	0	0	—	No	69	59	100	14	14*	—	3
Edwards et al[33]	United Kingdom	Stoma type	65	70	6.5	—	—	—	No	100	70	100	—	4*	—	4
Sailer et al[34]	Europe	Colonic J-pouch	65	63	9	0	0	17	No	100	64	100	6	11	—	3
Ho et al[35]	Asia	Colonic J-pouch	67	60	7.4	0	0	23	No	100	88	100	6	8*	—	1
Marijnen et al[36]	Europe	Preop radiation (short)	64	65	7.5	100	0	0	No	60	695	63	6	—	11	4
		Surgery only	64	63	7.5	0	0	—	No	53	719	65	6	—	12	3

(Continued)

TABLE 1. (*Continued*)

Study	Origin	Study Cohorts	Age	Sex	Height (cm)	Radiation: Short Preop	Radiation: Long Preop	Radiation: Postop	Laparoscopy	Stoma	Patients	Anastomosis	WI Rate	Leak Rate	Pelvic Sepsis Rate	Death Rate
Law et al[37]	Asia	Stoma type	67	61	6.6	—	—	—	No	100	80	100	—	5	—	3
Heah et al[38]	Asia	Colonic J-pouch	64	52	6.5	—	—	—	No	100	88	100	3	3	5	0
Machado et al[39]	Europe	Colonic J-pouch	67	59	10	78	0	0	No	1	100	100	1	—	9	1
Sauer et al[40]	Europe	Preop radiation (long)	62	71	5.8	0	100	0	No	—	415	69	—	11	—	1
		Postop radiation	62	66	6.8	0	0	72	No	—	384	71	—	12	—	1
Zhou et al[41]	Asia	Lap. surgery	44	56	4	—	—	—	Yes	—	82	100	—	1	1	0
		Open surgery	45	48	4	—	—	—	No	—	89	100		3	3	0
Gerard et al[42]	Europe	Preop radiation (boost)	68	65	4	0	100	0	No	—	81	53	—	12	—	1
Jiang et al[43]	Asia	Colonic J-pouch	64	56	8.3	—	—	—	No	33	56	100	—	4	—	0
Guillou et al[44]	United Kingdom	Lap. surgery	69	56	—	—	—	—	Yes	—	253	66	12	16	—	—
		Open surgery	69	54	—	—	—	—	No	—	128	62	13	11	—	—
Park et al[45]	Asia	Colonic J-pouch	58	58	4	—	—	58	No	100	50	100	1	1	1	0
Nowacki et al[46]	Europe	Antibiotic sponge	62	57	7.4	27	27	0	No	0	218	76	7	12	16	1
Bujko et al[47]	Europe	Preop radiation (short)	60	65	6.3	98	1	0	No	16	155	55	—	10	14	1
		Preop radiation (long)	59	66	6.3	4	97	0	No	17	157	55	—	9	13	1
Bosset et al[48]	Europe	Chemotherapy	63	73	6	0	100	0	No	—	979	53	—	—	—	2
Bulow et al[49]	Europe	Anastomotic stent	68	59	10	0	0	—	No	46	194	100	—	13	—	—
Gerard et al[50]	Europe	Chemotherapy	64	66	5	0	97	0	No	72	719	51	—	8	—	2
Lee et al[51]	Asia	Stapler type	—	—	—	—	—	—	No	—	50	100	—	6	—	—
Fazio et al[52]	North America	Colonic J-pouch	60	70	4	0	58	—	No	—	364	100	3	5	—	—
Matthiesen et al[53]	Europe	Stoma	68	61	10	81	0	—	No	99	116	100	—	—	10	1
		No stoma	68	49	10	77	0	—	No	1	118	100	—	—	28	0
Fujita et al[54]	Asia	Antibiotics	60	60	—	—	—	—	No	—	136	98	10	—	—	—
Braga et al[55]	Europe	Lap. surgery	63	66	9.1	0	15	—	Yes	29	85	87	7	9	15	1
		Open surgery	65	75	8.6	0	15	—	No	29	83	85	16	8	17	
Folkesson et al[56]	Europe	Stapler type	—	58	—	—	—	—	No	—	519	100	—	8	—	—
DeLaTorre et al[57]	Europe	Chemotherapy	64	69	6	0	100	—	No	—	144	59	—	9	—	1
Valentini et al[58]	Europe	Chemotherapy	64	63	5	0	100	0	No	—	164	79	—	9	—	1

Year is the year of publication; origin is the area where the study was designed and most patients recruited; study cohorts represents the randomization variable used (the cohorts were collapsed if the randomization variable was not one of the variables of interest); age is the patient mean age in years; sex is the percentage of males; height is the median height of the rectal cancers from the anal verge (cm); radiation is the percent of patients given that modality: short preop is 5 to 7 days of 20 to 30 Gy followed by surgery within 7 to 10 days, long preop is around 6 week of radiation (approximately 50 Gy) followed by surgery after at least 5 week wait; laparoscopy indicates whether surgery was laparoscopic-assisted; stoma is the percentage of patients with an anastomosis that received a protecting stoma; patients is the total number of patients recruited to the study; anastomosis is the percentage of the total patients that had an anastomosis at the end of their surgery.

Wound infection (WI) rate is the percentage of the total number of patients that had an abdominal wound infection; leak rate is the percentage of patients with an anastomosis diagnosed with an anastomotic leak; pelvic sepsis rate is the percentage of patients with an anastomosis that were diagnosed with either an anastomotic leak or a pelvic abscess; death rate is the percentage of patients that died postoperatively during their hospital stay.

*Study used routine radiological investigations.

TABLE 2. Prospective Cohort Studies Describing the Postoperative Complications of Surgical Removal of the Rectum to Treat Cancer

Study	Origin	Study Variable	Age	Sex	Height (cm)	Radiation: Short Preop	Radiation: Long Preop	Radiation: Postop	Laparoscopy	Stoma	Patients	Anastomosis	WI Rate	Leak Rate	Pelvic Sepsis Rate	Death Rate
Robles Campos et al[59]	Europe	Perineum after APR	63	53	—	—	—	—	No	—	102	0	18	—	—	—
Kessler et al[60]	Europe	Surgical mortality	65	—	—	0	10	—	No	18	965	66	—	8	14	4
Petrassi et al[61]	Europe	Stapler function	68	60	—	—	—	—	No	7	544	100	—	13*	—	1
Lothian and Borders[62]	United Kingdom	Population audit	—	—	—	0	5	12	No	—	251	71	—	9	—	—
Arbman et al[63]	Europe	Population audit	72	41	—	0	0	0	No	12	184	59	7	7	—	2
Miller and Moritz[64]	Europe	Stapler technique	67	50	—	—	—	—	No	—	103	100	—	4	—	4
Ichikawa et al[65]	Asia	Preop radiation (short)	56	83	4	0	100	—	No	—	35	66	—	17	—	0
		Surgery only	65	49	4	0	0	—	No	—	41	68	—	14	—	0
Lele et al[66]	United Kingdom	Preop radiation (short)	68	80	—	100	0	—	No	—	100	46	8	15	—	3
Chan et al[67]	North America	Preop chemoradiation	64	75	5	0	99	17	No	—	156	40	—	6	—	0
Pucciarelli et al[68]	Europe	Preop chemoradiation	60	61	6.5	0	100	—	No	79	51	84	6	12	14	0
Bosset et al[69]	Europe	Preop chemoradiation	65	76	5	0	100	—	No	—	60	58	—	3	—	0
Ngan et al[70]	Australia/NZ	Preop chemoradiation	59	67	7	0	100	0	No	96	82	61	—	6	8	0
Tang et al[71]	Asia	Colorectal SSIs	—	—	—	—	—	—	No	—	1926	88	2	2	3	—
Luna-Perez et al[72]	North America	Preop chemoradiation	55	56	6.5	0	100	0	No	23	68	100	7	10	12	—
Allal et al[73]	Europe	Preop radiation (long)	63	64	7.5	—	—	—	No	46	50	80	4	5	8	2
Marusch et al[74]	Europe	Stoma use	65	56	9.1	0	5	—	No	31	1431	34	5	11	13	1
Schiedbach et al[75]	Europe	Outcomes	67	48	—	—	—	—	Yes	—	380	61	7	14	—	2
Feliciotti et al[76]	Europe	Lap. surgery	64	55	—	0	92	—	Yes	12	81	74	—	18	—	0
		Open surgery	66	53	—	0	88	—	No	18	43	63	—	19	—	0
Zhou et al[77]	Asia	Outcomes	44	56	5	—	—	—	Yes	0	82	100	—	1	1	0
Morino et al[78]	Europe	Outcomes	64	62	6.1	—	—	—	Yes	47	100	100	4	17	—	2
Smith et al[79]	United Kingdom	Surgical outcomes	—	—	—	—	—	—	No	42	1346	49	—	8	—	—
Bulow et al[80]	Europe	Surgical outcomes	69	61	7.9	—	—	—	No	48	311	68	—	15	—	7
Delgado et al[81]	Europe	Outcomes	67	66	8.7	0	59	0	Yes	48	220	75	4	7	9	1
Hida et al[82]	Asia	Colonic J-pouch	61	63	—	—	—	—	No	—	94	100	—	10	—	—
Rose et al[83]	Europe	Outcomes	64	—	—	—	—	—	Yes	—	702	71	—	10	—	—
Fernandez-Martos et al[84]	Europe	Preop chemoradiation	65	63	5	0	100	0	No	—	91	47	—	12	—	1
Morino et al[85]	Europe	Lap. surgery	65	60	7	—	—	—	Yes	38	98	76	—	14	—	1
		Open surgery	61	61	7	—	—	—	No	31	93	63	—	5		2
Gastinger et al[86]	Europe	No stoma	66	55	9.6	0	4	—	No	0	1848	100	—	14	—	2

(*Continued*)

TABLE 2. (*Continued*)

Study	Origin	Study Variable	Age	Sex	Height (cm)	Radiation: Short Preop	Radiation: Long Preop	Radiation: Postop	Laparoscopy	Stoma	Patients	Anastomosis	WI Rate	Leak Rate	Pelvic Sepsis Rate	Death Rate
		Stoma	65	63	7.9	0	14	—	No	100	881	100	—	15	—	1
Alves et al[87]	Europe	Surgical outcomes	66	59	5	—	—	—	No	68	238	63	8	11	—	3
Schiedeck et al[88]	Europe	Outcomes	67	—	—	—	—	—	Yes	—	52	100	—	6	—	—
Tang and Seow-Choen[89]	Asia	Rectal to detect leak	62	60	—	—	—	—	No	100	195	100	—	17*	—	1
Widder et al[90]	Europe	Preop radiation (short)	65	65	6	100	0	0	No	70	184	72	—	11	17	1
Barlehner et al[91]	Europe	Surgical outcomes	65	64	8.9	0	52	6	Yes	—	194	91	2	14	15	0
Bretagnol et al[92]	Europe	Outcomes	63	61	5.5	0	83	—	Yes	—	144	100	—	—	23	1
Sihotsky et al[93]	Europe	Hypoxia for radiation	53	—	—	100	0	—	No	—	110	55	9	7	11	1
Ohwada et al[94]	Asia	Tegafur suppository	64	63	—	0	0	0	No	0	129	60	13	9	—	0
Lim et al[95]	United Kingdom	Radiology for leaks	—	60	—	—	—	—	No	87	138	100	—	17*	—	—
Konishi et al[96]	Asia	Surveillance for SSIs	59	69	—	0	19	—	No	—	217	58	18	—	—	—
Ptok et al[97]	Europe	Lap. surgery	66	59	9	0	10	47	Yes	—	237	70	—	13	—	1
		Open surgery	67	59	9	0	7	47	No	—	6952	70	—	12	—	2
Millan et al[98]	Europe	Intramucosal pH	66	56	8.8	—	—	—	No	6	90	100	14	11*	—	2
Wiltshire et al[99]	North America	Preop chemoradiation	63	60	6.3	0	100	0	No	—	121	57	18	—	—	0
Wong et al[100]	Asia	Lap. surgery	67	46	3	—	—	—	Yes	—	71	0	3	—	—	0
		Open surgery	68	58	4	—	—	—	No	—	31	0	16	—	—	0
Pappalardo et al[101]	Europe	Stoma use	64	51	8	0	25	—	No	0	224	98	—	7	—	0
Veenhof1 et al[102]	Europe	Outcomes	67	56	8	44	4	—	Yes	53	50	68	8	15	15	2
Palanivelu et al[103]	Asia	Outcomes	58	52	—	—	—	—	Yes	—	170	100	2	6	—	0
Kiyomatsu et al[104]	Asia	Preop radiation	60	75	4.3	0	98	—	No	12	221	50	14	14	52	0
Fukunaga et al[105]	Asia	Outcomes	66	66	—	—	—	—	Yes	0	74	89	5	11	—	0
Vermaas et al[106]	Europe	Preop radiation	67	59	6.9	60	16	—	No	57	521	58	—	10	—	3
Veenhof et al[107]	Europe	Preop radiation wait	65	69	5	100	0	0	No	52	108	43	7	20	39	4
Tjandra et al[108]	Australia/NZ	Outcomes	62	44	7	0	27	—	Yes	100	63	100	5	3*	—	—
Huh et al[109]	Asia	Outcomes	56	62	3.5	0	49	—	No	—	87	49	5	2	—	0
Lee et al[110]	Asia	Preop radiation (long)	55	83	4.5	0	100	0	No	57	57	74	2	2	5	0
de Bruin et al[111]	Europe	Preop radiation (long)	61	68	4.8	0	100	0	No	—	60	42	—	4	—	—

Year is the year of publication; origin is the area where the study was designed and most patients recruited; study variable represents the main variable of the study (the cohorts were collapsed if this variable was not one of the variables of interest); age is the mean age in years; sex is the percentage of males; height is the median height of the rectal cancers from the anal verge (cm); radiation is the percent of patients given that modality: short preop is 5 to 7 days of 20 to 30 Gy followed by surgery within 7 to 10 days, long preop is around 6 week of radiation (approximately 50 Gy) followed by surgery after at least 5 week wait; laparoscopy indicates whether surgery was laparoscopic-assisted; stoma is the percentage of patients with an anastomosis following their extirpative surgery that received a protecting stoma; patients is the total number of patients recruited to the study; anastomosis is the percentage of the total patients that had an anastomosis at the end of their operation.

Wound infection (WI) rate is the percentage of the total number of patients that had an abdominal wound infection; leak rate is the percentage of patients with an anastomosis diagnosed with an anastomotic leak; pelvic sepsis rate is the percentage of patients with an anastomosis that were diagnosed with either an anastomotic leak or a pelvic abscess; death rate is the percentage of patients that died postoperatively during their hospital stay.

*Study used routine radiological investigations.

TABLE 3. Complication Rates of Rectal Cancer Surgery

Complication	Rate*	95% CI	No. Studies	I^2 Value	Sensitivity Analysis†
Wound infection	0.07	0.05–0.08	50	90%	0.06
Anastomotic leak	0.11	0.10–0.12	84	70%	0.10
Pelvic sepsis	0.12	0.09–0.16	29	93%	0.12
Postoperative death	0.02	0.02–0.03	75	70%	0.02

*Complication rates were obtained from prospectively conducted studies using the random effects model; the 95% confidence interval and the number of studies available for analysis are shown; I^2 value is the measure of study heterogeneity.

†Sensitivity analysis shows the complication rates obtained if studies classified as case series are included in the analysis.

TABLE 4. Prospective Studies Describing the Continence Functional Results of Surgical Removal of the Rectum to Treat Cancer

				Radiation								
Study	Type	Study Cohorts	Height	Short Preop	Long Preop	Postop	Eligible Patients	Patients Assessed	F/U	Main Outcome		Comment
Halbook et al[25]	RCT	Colonic J-pouch	7	27	0	6	52	47	12	Miller score/18	2	16% had nocturnal bowel movements
		Straight	7	16	0	8	45	42			5	
Ho et al[35]	RCT	Colonic J-pouch	7.2	0	0	9	44	32	12	Wexner score	No change	12% had nocturnal leak
		Colopasty	7.6	0	0	36	44	36				
Heah et al[38]	RCT	Sigmoid vs. descending pouch	6.5	—	—	—	88	38	12	Not specified	—	3% required pad
Machado et al[39]	RCT	Colonic J-pouch	10	81	0	0	36	36	24	Miller score/18	5	36% required pad
		Side-to-end	10	80	0	0	35	35			6	
Jiang et al[43]	RCT	Colonic J-pouch	7.9	—	—	—	24	22	24	Not specified	—	8% required pad
		Side-to-end	8.6	—	—	—	24	16			—	
Park et al[45]	RCT	Colonic J-pouch	3.9	0	0	50	26	22	12	FISI score	19	
		Straight	4.0	0	0	65	24	16			28	
Bosset et al[48]	RCT	Chemotherapy	6	0	100	0	522	522	65	Overall survival	—	9% had fecal incontinence
Fazio et al[52]	RCT	Coloplasty	4.0	58	—	—	47	38	24	SF-36 (FISI score shown)	39	63% required pad
		Straight					49	35			40	
		Colonic J-pouch					137	115			31	
		Coloplasty					131	109			37	
Chan et al[67]	Cohort	Preop chemoradiation	5	0	99	17	62	?	60	Oncologic outcomes	—	6% had intermittent soilage
Luna-Perez et al[72]	Cohort	Preop chemoradiation	6.5	0	100	0	68	68	24	Oncologic outcomes	—	3% had anal incontinence
Hida et al[82]	Cohort	Colonic J-pouch	—	38	0	23	52	48	12	Function score/26	3–6	
		Straight	—	9	0	5	86	80			3–10	
Barlehner et al[91]	Cohort	Surgical outcomes	8.9	0	52	6	176	176	46	Not specified	—	1% had fecal incontinence

Year is the year of publication; type is the design of the study: randomized controlled study (RCT) or prospective cohort study; study cohorts represents the cohorts within the study or the variable according to which the patients were segregated; height is the median height of the rectal cancers from the anal verge in centimeters; radiation is the percent of patients given that modality: short preop is 5 to 7 days of 20 to 30 Gy followed by surgery within 7 to 10 days, long preop is around 6 week of radiation (approximately 50 Gy) followed by surgery after several weeks wait; eligible patients represents the total patients in the study that had an anastomosis; patients assessed represents the number of patients that had functional assessment; F/U is the length of follow-up in months; main outcome is given as stated in the study paper.

reported anastomotic leak rates. Although age and method of detection of anastomotic leaks seem to have an expected effect (studies with older patients and studies that use routine radiologic tests have higher reported rates of anastomotic leaks), the average height from anal verge shows an effect that is opposite to the expected one (studies with lower tumors show a lower rate of anastomotic leak). Studies that used laparoscopic-assisted surgery versus open surgery did not report different rates of pelvic sepsis (13 [10, 22] vs. 13 [10, 17]) or of wound infection (5 [3, 8] vs. 7 [6, 9]).

The variables that are significant and explain some of the heterogeneity in the reported postoperative death rates are year of publication, study origin, average age, and use of laparoscopy, whereas average tumor height and preoperative radiation use are not significant. The relatively large postoperative death rate reported in studies from the United Kingdom is significantly different from the death rate reported in studies from Continental Europe, Asia, and shows no difference from the death rate reported in North American and Australia/New Zealand studies probably because the latter areas

TABLE 5. Effect of Covariables on Complication Rates of Rectal Cancer Surgery

Variable*	Anastomotic Leak	$P^\dagger$	Postoperative Death	$P^\dagger$
Year of publication				
Up to 2002	0.11 (0.09, 0.13)	—	0.03 (0.02, 0.04)	0.01‡
2003 and later	0.11 (0.10, 0.12)		0.016 (0.01, 0.02)	
Study origin				
Europe	0.11 (0.11, 0.12)	NS	0.02 (0.02, 0.03) }	<0.001§
Asia	0.07 (0.05, 0.10)		0.01 (0.01, 0.02) }	
UK	0.13 (0.10, 0.17)		0.06 (0.04, 0.09) }	
Australia/NZ	0.05 (0.02, 0.11)		0.01 (0, 0.10)	
North America	0.09 (0.05, 0.16)		0.01 (0, 0.04)	
Age				
<65	0.10 (0.08, 0.11)	0.047‡	0.02 (0.01, 0.02)	0.048
≥65	0.12 (0.11, 0.13)		0.03 (0.02, 0.03)	
Height				
Low	0.09 (0.08, 0.11)	0.02	0.02 (0.01, 0.02)	—
High	0.12 (0.11, 0.13)		0.02 (0.02, 0.03)	
Preop radiation use				
No radiation	0.11 (0.10, 0.13)	NS	0.02 (0.02, 0.03)	NS
Short course	0.12 (0.10, 0.15)		0.03 (0.02, 0.05)	
Long course	0.10 (0.09, 0.13)		0.02 (0.01, 0.02)	
Use of laparoscopy				
Open surgery	0.11 (0.10, 0.12)	—	0.02 (0.02, 0.03)	<0.001
Laparoscopic-assisted surgery	0.11 (0.09, 0.14)		0.01 (0.01, 0.02)	
Stoma use				
<50%	0.12 (0.10, 0.13)	NS		
>50%	0.11 (0.09, 0.13)			
Method of detection				
Clinical	0.10 (0.09, 0.11)	0.016		
Radiological	0.13 (0.11, 0.16)			

*Covariables, except use of laparoscopy, were chosen a priori; the geographical regions and method of detection were defined a priori; cut-offs for year of publication, age, height (6.75 cm), preop radiation use (50%) and stoma use were chosen post-hoc and are the median values.

†Z-test was used to test significance of covariables; statistical significance was accepted when $P < 0.05/n$, where n was the number of pair wise comparisons.

‡Covariables remained significant in multivariable analysis (linear regression).

§All 3 pairwise comparisons in this group have a $P < 0.001$.

have few studies with large confidence intervals. The postoperative death rate shows a decrease in more recently published studies, an expected rise with increasing average age, and a decrease in the cohorts using laparoscopic-assisted surgery.

Multivariable models were developed using linear regression to include the variables that were significant in univariable analysis. Average tumor height and method of detection lost their statistical significance to predict anastomotic leak rate in a model incorporating average age, while study average age was the only variable that remained statistically significant. For postoperative death rate, year of publication remained the only variable that retained its statistical significance in a model incorporating average age, study origin, and use of laparoscopy; the studies from the United Kingdom that reported a high postoperative death rate were published early and had high average ages. The studies that included patients treated with laparoscopic-assisted surgery were published more recently, which explains their lower observed postoperative death rates.

DISCUSSION

The postoperative complication rates of rectal cancer surgery involving removal of the rectum have been determined using data from a large number of prospective studies published in the last 2 decades in a variety of clinical settings. The observed wound infection rate was 7% (95% CI: 5,8), the anastomotic leak rate was 11%,[10,12] the pelvic sepsis rate was 12%,[9,16] and the postoperative death rate was 2%.[2,3] This review is the largest such available in the literature that examines the complications of rectal cancer surgery. These findings may be used to inform patients about the likelihood of complications following their surgery, as benchmark values for quality improvement initiatives, and for sample size calculations in the design of future studies.

The results of this systematic review are accurate, precise, and applicable to a wide range of clinical situations. Only prospective studies have been included in the review so that the estimates of the event rates are unlikely to be underestimated. The number of studies that have been found and included has yielded very large numbers of cases and patient events for analysis. This has led to tight confidence intervals around the point estimates of the complication rates and has led to very robust results: it would take large numbers of cases and events with different complication rates to change these results. The studies included in the analysis have a wide range of characteristics including origin, patient characteristics, and interventions so that the findings of this review should be applicable to an equally large variety of clinical situations.

Pelvic sepsis is not as widely used outcome as anastomotic leak and is poorly reported, which makes its interpretation difficult. This outcome is needed in this review, however, to reconcile the data between studies with different definitions of anastomotic leak. The pelvic sepsis rate may be slightly overestimated because it is calculated for cases with an anastomosis, but includes abscesses from cases without an anastomosis (ie, APR). This bias is small because there are few pelvic abscesses following APR that are not associated with perineal wound infection or breakdown. Dichotomization of the covariables in the univariable analysis may have impeded our ability to detect covariable effects on the anastomotic leak rate and postoperative death rate, but it allowed us to use the results of the random effects model for the comparisons. North American cases are underrepresented in this review due to a dearth of available studies (only 5% of the sample). The anastomotic leak rate in the North American studies falls between that of Asian studies and European studies, which are the most numerous, and the postoperative death rate is very similar to either, and so the results of this review should be applicable in North America as well. The very broad inclusion of studies may impede applicability of the results in very specific clinical situations. The complication rates seen in this review may be used by clinicians and patients as guides to the expected risks of complications, but only in the most general terms; there are factors that modify the complication risks in every specific case.

The data available on fecal incontinence are generally poor. Most of the studies available examine the relative benefits of colonic J-pouch versus straight anastomosis for reconstruction following the extirpation of rectal cancer. The measures used for fecal incontinence were oftentimes complex and hard to interpret. More importantly, the studies used a variety of outcomes measures, so that comparison between them is impossible. There is a large unmet need for prospective studies on rectal cancer treatment to report on the functional outcomes after surgery using a common outcome measure, preferably one that is clinically applicable.

The subgroup analysis of the anastomotic leak rates and postoperative death rates has yielded some interesting results. Average age, median height from anal verge, and method of detection are significant variables with respect to anastomotic leak. The surprising finding is that the studies with smaller median height from anal verge have also lower rates of anastomotic leak, which illustrates the problem of using patient variables in comparisons among studies. The studies with lower tumors must have had other characteristics to explain their lower anastomotic leak rate and that seems to be indicated by the multivariable analysis, which shows that height and method of detection lose their statistical significance when incorporated in a model together with average age. The postoperative death rate has decreased in recent studies, increased among studies with older patients, decreased in studies including patients who had laparoscopic-assisted surgery rather than open surgery, and surprisingly large among studies from the United Kingdom. The large postoperative death rate seen in the United Kingdom studies is at least partially explained by the fact that the studies from that region are relatively old and have older patient populations, as shown in the multivariable analysis. The use of laparoscopy also loses significance with respect to postoperative death rate in the multivariable model, because of the association between this variable and the year of publication: most studies including patients who had laparoscopic-assisted surgery were published in the latter period of this review. The conclusions of the multivariable analysis need to be interpreted with caution, however, because the models do not incorporate the sizes of the respective trials, but only the estimates of the complication rates.

CONCLUSION

Benchmark complication rates for radical rectal cancer surgery have been obtained for use in sample size calculations in future studies and for quality control purposes. Postoperative death rates have decreased in more recent studies.

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