This is a non-final version of an article published in final form in **Diseases of the Colon & Rectum:** September 2018 - Volume 61 - Issue 9 - p 1016–1025
doi: 10.1097/DCR.0000000000001158

Link to publishers website

Recurrence Risk after Up-to-Date Colon Cancer Staging, Surgery and Pathology: Analysis of the Entire Swedish Population

Running title: Up-to-Date Colon Cancer Recurrence Risk

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Conflicts of interests: The authors have no conflicts of interest to report

Funding: This work was supported by the Swedish Cancer Society, grant number CAN 2016/447**.**

Previous presentations: No previous presentation.

Word count (According to Microsoft Office Word for Mac 2017)

Manuscript: 2,958 (excluding abstract, references, tables, legends, and figures)

Abstract: 299

Authors' contributions: EO contributed with the statistical analyses. BG contributed with the acquisition of data. Both authors contributed with the design, interpretation, text, critical revision and final approval of the manuscript.

Category: Colorectal Neoplasia

Abstract

Background: Developments in the quality of care of patients with colon cancer have improved surgical outcome and thus the need for adjuvant chemotherapy.

Objective: To investigate the recurrence rate in a large population-based cohort after modern staging, surgery and pathology have been implemented.

Design: Retrospective registry study.

Setting: Data from patients included in the Swedish Colorectal Cancer Registry covering 99% of all cases, and undergoing surgery for colon cancer stages I-III between 2007 and 2012 were obtained.

Patients: In total, 14,325 patients, who did not receive any neoadjuvant treatment underwent radical surgery and were alive 30 days after surgery, were included.

Main Outcome Measure: Tumor and node classification and National Comprehensive Cancer Network defined risk factors for recurrence were used to assess overall and stage-specific five-year recurrence rates.

Results: The median follow-up of non-recurrent cases was 77 months (range 47-118). The five-year recurrence rate was 5% in stage I, 12% in stage II and 33% in stage III patients. In patients classified as pT3N0 with no or one risk factor, the 5-year recurrence rate was 9% and 11%, respectively. Risk factors for shorter time to recurrence were male sex, more advanced pT- and pN- classification, vascular and perineural invasion, emergency surgery, lack of central ligature, short longitudinal resection margin, post-operative complications, and, in stage III, no adjuvant chemotherapy.

Limitations: The registry does not contain some recently identified factors of relevance for recurrence rates and some late recurrences may be missing.

Conclusion: The recurrence rate is less than that previously observed in historical materials, but current, commonly used risk factors are still useful in evaluating recurrence risks. Stratification by pT-, pN- classification and the number of risk factors enables the identification of large patient groups characterized by such a low recurrence rate that it is questionable whether adjuvant treatment is motivated.

Background

Colon cancer survival has improved with advances achieved in treatment and care.[1,2] The introduction of adjuvant chemotherapy during the 1990s and subsequent refinements in the protocols and selection of patients who receive chemotherapy explain at least partly these improvements.[3–5] Surgical techniques have improved with the introduction of central vascular ligature and complete mesocolic excision, which, together with more careful dissection of the surgical specimen and increasing lymph node yields, have resulted in improved staging, and ultimately survival.[6–9] Examples of other activities aimed at improving the results even further are quality assurance measures[10,11] and improvements in pre- and post-operative care.[12]

In a systematic review that included published articles from 2005-2013, the outcome after radical surgery in stage II and III colon cancer patients was described with the aim to define a more exact need for adjuvant chemotherapy.[13] Firm conclusions could not be drawn due to few studies being identified, although it would appear as if the improvements in the quality of care, surgery and staging reduced recurrence risks (5-year disease-free survival (DFS) was 81%), thus decreasing the need for adjuvant therapy in all stages. Currently, National Comprehensive Cancer Network (NCCN) guidelines cite data mainly published during the early years of the first decade of this century, in which DFS in T3N0 disease was 73% if no adjuvant treatment was administered.[14] Japanese and European guidelines report 13% and 20% recurrence rates in stage II disease, respectively.[15,16] In stage III, the prognosis varies with estimates ranging from 13% for very low-risk patients with a single positive node[17] to considerably higher percentages for patients with tumors with high-risk features.[3,15] Further risk stratification and knowledge of recurrence rates in modern patient materials are required so that clinicians in the future can avoid treatment decisions based on recurrence rates obtained from old series, as is the case with existing guidelines and nomograms.[3–5,14,15,17,18]

Aim and hypothesis

The aim was to investigate the recurrence rate and survival in a population-based cohort stratified by TNM status and parameters relevant to recurrence, including those recommended by NCCN and ESMO.

The main outcome measure was the recurrence rate in stage I-III patients, who had been radically operated and

survived surgery. A secondary aim was to validate common clinical risk factors of recurrence to describe the recurrence risks in subgroups used clinically.

Our main hypothesis was that the recurrence rate in large patient groups is low and that it has decreased (i.e. increased time to recurrence, TTR) compared with historic materials. A secondary hypothesis was that commonly used risk factors of recurrence are still valid and can stratify patients into groups with markedly different risks of recurrence.

Patients and methods

The regional ethical research committee at the University of Uppsala, Uppsala, Sweden approved the study, 2013/093/1.

Material

Patient data from the SCRCR were requested for all colon cancer patients diagnosed between 2007 and 2012 with stage I-III disease, n=16,659. A cohortogram with the selection and exclusion of patients is presented in Figure 1. The final size of the cohort was 14,325 patients who received no neoadjuvant treatment, underwent radical surgery and were alive 30 days after surgery.

Outcomes, TTR and overall survival (OS) were defined according to Punt et al.[19] Tumors were classified according to TNM 7.[20]

Factors of primary interest (major factors) were age, sex, tumor side, emergency surgery, pT-classification,[5,21] pN-classification, lymph node retrieval and number of positive nodes, malignancy grade, vascular and/or perineural invasion, mucinous features, post-operative complications and whether adjuvant treatment was initiated or not. The pT3 category was sub-classified by the depth of invasion into the pericolic tissue, <5 mm (ab) and ≥5 mm (cd).[22] Complications were defined in the registry as events requiring additional medical or surgical treatment during the post-operative period or within 30 days of surgery. Co-morbidity was recorded as body mass index (BMI) and the American Society of Anesthesiologists' (ASA) classification.

In order to investigate the quality of care, all pre-therapeutic investigations of the tumor, lungs and liver, margins of resection, central vascular ligature (ligation at the branching of the ileocolic, right or middle colonic artery from the superior mesenteric artery or ligation of the inferior mesenteric artery at the aorta) and adequate lymph node sampling (>12) were implemented as factors.[16] The year in which the surgery was carried out was used to investigate differences in the follow-up time and number of recurrences.

Statistics

The distribution of clinical parameters and outcomes were compared. Risk factors of recurrence according to NCCN guidelines were used to stratify patients into groups according to pT-classification, pN-classification and

the number of risk factors (pT4, emergency surgery, high-grade malignancy, vascular or perineural invasion, inadequate lymph node sampling).[5] The net probability of recurrence within five years was calculated for the groups, which were further grouped according to whether they received adjuvant treatment or not. Kaplan-Meier curves were drawn for stage II and III with the outcome TTR stratified by the number of risk factors. Differences were tested with the log-rank test.

Univariable and multivariable Cox proportional hazards models were used to calculate unadjusted and adjusted hazard ratios (HR), and 95% confidence intervals (CI) for TTR and OS.

Terms with statistically significant differences in the univariable analyses were included in the multivariable analyses. The distribution of stage II and III disease, emergency surgery, measures of quality of care and chemotherapy were compared for each year of surgery. Distributions were tested with the 2-sided asymptotic Pearsons-$\chi 2$. All statistical calculations were performed using IBM SPSS Statistics version 24.0. Differences were considered statistically significant if p was less than 0.05.

Results

The median age of the cohort was 74 years (mean 72 years, range 17-101 years). The median follow-up time for patients without a recurrence or a terminal event was 77 months (range 47-118). The characteristics of the cohort, risk factors and distribution of recurrences and mortality are presented in Table 1 (major factors) and supplementary Table 1 (additional factors). In the entire patient material, recurrences were seen in 16 % of the patients, predominantly at distant sites. The local recurrence rate was 4% overall with no major difference according to patient and tumor characteristics, except when the tumor was classified as pT4 or pN2 (10-11%). Emergency surgery, pT4-classification, pN2b-classification, vascular and/or perineural invasion were characteristics indicating the highest risk of overall and distant recurrence. The mortality rate was higher in underweight patients.

Risk of recurrence according to stage and number of risk factors

A comparison of five-year recurrence rates factored by pTN-classification and NCCN risk factors is presented in Table 2. Stage I patients had a 5% five-year recurrence rate. In stage II patients, the overall recurrence rate was 12%, ranging from 9% (95%CI 7-11%) in pT3N0 with 0 risk factors to 31% (95%CI 23-39%) in pT4N0 with more than 2 risk factors. In patients in whom a subdivision of the pT classification was possible, the recurrence rate was 9% (95%CI 7-11%) in pT3ab and 12% (95%CI 10-14%) in pT3cd. In pT3N0 disease, no difference was seen for 0 and 1 risk factor while, in pT4N0 disease, 1 or more risk factors were equally bad and the prognosis poorer than if no risk factor was present.

Stage III patients had a five-year recurrence rate of 33%, ranging from 17 to 44%. In pT1-3N1 disease, there was a positive correlation between an increase in the number of risk factors and the recurrence risk. Patients with pT4N1 or pN2 disease and more than 2 risk factors had the poorest prognosis. In stage II, the recurrence rate did not differ with adjuvant chemotherapy while lower rates were seen in patients receiving adjuvant chemotherapy in the pT4N1 group with more than 2 risk factors and in all patients with pT1-3N2-disease. Kaplan-Meier curves for stage II and stage III patients according to the number of risk factors are presented in Figure 2A and 2B.

Importance of risk factors for time to recurrence

Unadjusted HRs for TTR are presented in Table 3 for major factors with additional factors presented in supplementary Table 2. Stage II patients receiving adjuvant treatment had an higher recurrence risk while stage III patients receiving adjuvant treatment had a lower recurrence risk. The year of surgery did not impact on the TTR.

In the multivariable analyses (Table 4), factors correlating with an increased risk for recurrence were male sex, emergency surgery, distal ligature, or no reported ligature, pT- and pN-classification, vascular and perineural invasion and post-operative complications. For each positive node in stage III the HR increased by 1.02 (95%CI 1.01-1.03). Adjuvant treatment correlated with a lower risk of recurrence. Right-sided stage II tumors had a lower risk of recurrence (HR 0.8, 95%CI 0.7-1.0, p=0.033) whereas there was no difference in stage III between right- and left-sided lesions.

Importance of risk factors for overall survival

Factors correlating with decreased OS in the uni- and multivariable Cox proportional hazards models are presented in Table 3, and supplementary Tables 2 and 3. They were male sex, emergency surgery, advanced pT- and pN-classification, high-grade malignancy, vascular and perineural invasion, low lymph node yield, more positive nodes, post-operative complications, greater age, low BMI (<18.5), surgery in health care regions 4 and 5, and a high ASA classification. Better survival was seen in patients with pre-therapeutic staging of the tumor, an intermediate longitudinal resection margin and in those who received chemotherapy. Stage III patients with right-sided tumors had poorer overall survival in the stage-stratified multivariable analysis, HR 1.1 (95%CI 1.0-1.3, p=0.009).

Quality of care

Changes in aspects related to quality of care between 2007 and 2012 are presented in supplementary Table 4. Utilization of pre-therapeutic staging in the elective group increased. Excluding missing data, the proportion of

resections with a lateral/circumferential margin over 10 mm increased while the proportion of resections with less than 3 mm decreased. No change was seen as regards the longitudinal margin of resection. Report of a vascular ligature increased, but the proportion of patients with central vascular ligature did not change. The proportion of patients with an adequate number of sampled lymph nodes (≥12) increased as did the mean number of sampled lymph nodes, from 16 to 23.

The mean number of positive lymph nodes in stage III and the proportion of patients in different stages did not change.

The use of adjuvant chemotherapy in stage III increased from 56% to 63%, no change was seen in stage II overall, but an increase in the use of adjuvant treatment was seen in pT4N0 patients. Data on the type of chemotherapy used was available for 76% of the patients; in these patients, a fluoropyrimidine with oxaliplatin was used in 37% of stage II patients and in 57% of stage III patients.

Discussion

The recurrence rate, which defines the need for, and thus the potential gain from adjuvant chemotherapy, is still well predicted by the regular UICC staging and by the pTN-classification. Stratification by NCCN risk factors reveals that the stages are heterogeneous but also that many patients today have a lower recurrence risk than presented in guidelines.[3–5,14,15] Patients with positive nodes administered adjuvant treatment had lower recurrence rates, indicating a benefit from the treatment; however, the purpose of the study was not to evaluate the value of treatment. The use of adjuvant chemotherapy was limited to 12% in stage II patients, thus having a limited influence on overall recurrence rates. However, since it was probably given selectively, it still disturbs the interpretations somewhat. At least 3 out of 4 (77%) stage II patients had a recurrence rate in the order of 10% (0 or 1 risk factor, no adjuvant treatment), and the remaining patients had a rate of 20-25% (2 or more risk factors or 0 or 1 risk factor if given adjuvant therapy). A 10% recurrence rate means that a fluoropyrimidine prevents 2 recurrences in 100 treated patients[23] and the addition of oxaliplatin prevents one more; these benefits are considered by most clinicians too small to merit general implementation. [24] If the absolute risk of recurrence is 20%, a fluoropyrimidine prevents 4-5 recurrences and the addition of oxaliplatin prevents 3 more; these are gains that many consider sufficient for implementing therapy, although not universally.[25] Adjuvant chemotherapy was used much more frequently in stage III patients, making estimations of recurrence rates without adjuvant therapy more difficult. The recurrence rate was 22% in 40% of the stage III patients (pT1-3N1, 0 or 1 risk factor, no adjuvant treatment) posing the question whether oxaliplatin supplementation is warranted.

The routinely used risk factors for recurrence were confirmed in the regression analyses, but additional information about the recurrence risk was gained from knowing whether post-operative complications occurred and how many lymph nodes were positive. Our findings further indicate that the pT3 sub-classification is of importance; however, it was not reported with sufficient accuracy, only as pT3ab versus pT3cd. It is likely that the prognostic importance of the pT-classification is not between pT1-2 and pT3-4, but rather within pT3, as reported in one previous study.[22] A pT4-sub-classification, again not completely reported, was of less importance, although peritoneal involvement (pT4a), entailed a poorer prognosis than overgrowth to other

structures (pT4b). The use of central vascular ligatures was associated with a lower recurrence risk compared with distal ligatures, confirming earlier observations and confirming that the surgical technique is of importance in achieving low recurrence rates.[7]

While it is well-established that right-sided tumors have a poorer survival when metastatic,[26] much controversy exists in primary colon cancer.[27–31] The lower recurrence risk for right-sided tumors in stage II (and similar survival) and a similar recurrence risk for stage III right- and left-sided tumors (but a poorer OS for right-sided tumors), indicate that recurrence risks, and thus the need for adjuvant therapy, do not differ according to tumor location, whereas OS does. An explanation for fewer recurrences in right-sided stage II tumors may be that mismatch repair (MMR) deficient tumors, with a lower risk of recurrence, are common (about 15-20%) in this group.[32] The SCRCR does not contain MMR data. The similar recurrence risk in stage III indicates that MMR-proficient tumors recur to the same extent in both locations, but that survival after recurrence is poorer in right-sided primaries.

The most important factor to consider for OS is the patient, i.e. comorbidities and age are more important than any tumor-related factor, when ranked by HR. Low BMI (<18.5) was also important, ranking directly after pT4 and pN2. Factors correlating with an increased risk of recurrence also correlated with a poorer OS. Differences in OS between health-care regions were small in adjusted analyses, but may warrant further study. A better OS was seen in patients receiving adjuvant treatment, probably reflecting both the influence on the recurrence risk and the performance status required to be administered adjuvant treatment.

Measurements indicating improved quality of care such as pre-therapeutic staging, margins of resection, lymph node yields and reporting to the registry have increased but the recurrence rates (and OS) did not correlate with the year of surgery. The average number of positive lymph nodes in stage III patients remained the same but more nodes were identified, indicating improved quality of the surgical specimen and the clinicopathological investigation. Even though lymph node yields increased, there was no obvious stage migration within our material (stage II to III).

Strengths and weaknesses

The SCRCR covers about 99% of the patients diagnosed with colon cancer in Sweden and survival is updated every week with the help of the National Death Registry. No exclusion based on co-morbidities and age was performed, consequently providing a truly population-based cohort of radically resected colon cancers.[33] All recurrences are to be reported to the SCRCR once they have occurred, or at least after 3 and 5 years when a request is sent to the responsible physician at the hospital where the patient was operated. For patients operated more than 5 years ago, missed recurrences are probably negligible, whereas it is possible that a few recurrences seen in patients with a follow-up of between 3 and 5 years may not yet have been registered. Most recurrences occur within 3 years after surgery.[34] Some variables of interest are not recorded, for example, carcino-embryonic antigen levels, known to predict recurrences,[35] and the RAS, BRAF and MMR-protein status, which are presently of great interest .

Prospects

To truly assess the recurrence risk in a modern material, an unselected population, to which no adjuvant treatment has been administered is desired. This is controversial and would need compelling evidence of both a low recurrence risk and a higher risk of harmful side-effects subsequent to adjuvant treatment. Several trials have investigated the safety and effects of three rather than six months of adjuvant treatment with a regimen containing oxaliplatin and reported less neurotoxicity with no significant inferiority in at least the low-risk groups.[36,37]

Conclusions

In the entire Swedish population of radically resected colon cancer patients during a recent 6-year period, recurrence rates are less than those seen in historical materials and presented in guidelines. However, current commonly used risk factors are still useful in predicting TTR. The results reflect real-world data, where surgery was performed at more than 50 hospitals in a population of just less than 10 million inhabitants. The stratification of patients by pTN-classification and NCCN risk factors reveals the prognostic heterogeneity of the disease and the complexity that clinicians are faced with when deciding whether to recommend adjuvant treatment and at what intensity level. The pT3 sub-classification seems to be an important prognostic factor in addition to those recommended by the guidelines.

It has proved possible to define a patient population with such a low risk of recurrence that it is questionable whether adjuvant treatment is motivated at all. It is also possible to identify subgroups, who are presently recommended oxaliplatin and in whom the possible gains from this addition are minimal and thus questionable.

Acknowledgements

The authors wish to thank the Swedish Colorectal Cancer Registry and all reporting contributors.

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Table 1: Distribution of characteristics (major factors), number of recurrences and mortality in the cohort

Parameter		**Total**		**Recurrence**			**Mortality**		
		No.	**(%)**	**No.**	**(%)**	**p[a]**	**No.**	**(%)**	**p[a]**
Total		14325		2305	(16)		5340	(37)	
Age	**< 75**	7629	*(53)*	1283	(17)	0.012	1779	(23)	0.000
	≥ 75	6696	*(47)*	1022	(15)		3561	(53)	
Sex	**Female**	6984	*(49)*	1195	(17)	0.001	2741	(39)	0.000
	Male	7341	*(51)*	1110	(15)		2599	(35)	
Side	**Right**	8030	*(56)*	1250	(16)	0.127	3167	(39)	0.000
	Left	6287	*(44)*	1053	(17)		2170	(35)	
	Unknown	8		2			3		
Surgery	**Elective**	12163	*(85)*	1698	(14)	0.000	4191	(34)	0.000
	Emergency	2162	*(15)*	607	(28)		1149	(53)	
pT	**pT1**	1181	*(8)*	45	(4)	0.000	277	(23)	0.000
	pT2	2016	*(14)*	142	(7)		644	(32)	
	pT3 all	8986	*(63)*	1456	(16)		3313	(37)	
	pT4 all	2056	*(14)*	653	(32)		1075	(52)	
	Missing	60	*(0)*	8	(13)		5	(8)	
pT3 [b]	**pT3ab**	3457	*(24)*	398	(12)		1086	(31)	
	pT3cd	2248	*(16)*	501	(22)		869	(39)	
	Unknown	3291	*(23)*	558	(17)		1364	(41)	
pT4 [b]	**pT4a**	534	*(4)*	181	(34)		257	(48)	
	pT4b	255	*(2)*	66	(26)		108	(42)	

	Unknown	1268	*(9)*	406	(32)		710	(56)	
pN [b]	**pN0**	8745	*(61)*	779	(9)	0.000	2845	(33)	0.000
	pN1	3346	*(23)*	716	(21)		1344	(40)	
	pN2a	1025	*(7)*	371	(36)		511	(50)	
	pN2b [c]	884	*(6)*	422	(48)		554	(63)	
	Missing	325	*(2)*	17	(5)		86	(26)	
UICC	**UICC I**	2730	*(19)*	120	(4)	0.000	770	(28)	0.000
	UICC II	6314	*(44)*	682	(11)		2160	(34)	
	UICC III	5201	*(36)*	1496	(29)		2383	(46)	
	Missing	80	*(1)*	7	(9)		27	(34)	
Sampled nodes	**<12 LN**	2544	*(18)*	409	(16)	0.010	1218	(48)	0.000
	≥12 LN	11356	*(79)*	1869	(16)		4006	(35)	
	Missing	425	*(3)*	27	(6)		116	(27)	
Malignancy	**Low-grade**	10709	*(75)*	1621	(15)	0.000	3799	(35)	0.000
	High-grade	2738	*(19)*	570	(21)		1220	(45)	
	Missing	878	*(6)*	114	(13)		321	(37)	
Vascular	**No**	9590	*(67)*	1162	(12)	0.000	3175	(33)	0.000
invasion	**Yes**	2635	*(18)*	815	(31)		1282	(49)	
	Missing	2100	*(15)*	328	(16)		883	(42)	
Perineural	**No**	9264	*(65)*	1248	(13)	0.000	3121	(34)	0.000
invasion	**Yes**	1191	*(8)*	409	(34)		591	(50)	
	Missing	3870	*(27)*	648	(17)		1628	(42)	
Adjuvant	**No**	10319	*(72)*	1242	(12)	0.000	4168	(40)	0.000
treatment	**Yes**	4006	*(28)*	1063	(27)		1172	(29)	

[a] Proportions tested with Pearsons-$\chi 2$ test.

[b] The pTN-classification was subdivided into pT3a-d, pT4a-b and pN2a-b whenever data were available

[c] pN2a: 4-6 positive nodes.

Table 2: Recurrence risk at 5 years after surgery (TTR) grouped according to UICC stage and pTN-classification, adjuvant treatment and the number of risk factors (RF)

		All				No adjuvant treatment				Adjuvant treatment			
				95% CI				95% CI [b]				95% CI [b]	
Stage	**RF [a]**	***No.***	***5y RR***	***Lower***	***Upper***	***No.***	***5y RR***	***Lower***	***Upper***	***No.***	***5y RR***	***Lower***	***Upper***
I	***0***	1342	5%	3%	7%	1330	5%	3%	7%	12	38%	9%	67%
	1	891	5%	3%	7%	874	5%	3%	7%	17	19%	-1%	39%
	≥2	118	5%	1%	9%	109	6%	2%	10%	9	0%	0%	0%
II	***0***	2862	9%	7%	11%	2743	9%	7%	11%	119	13%	7%	19%
	1	2147	11%	9%	13%	1836	11%	9%	13%	311	13%	9%	17%
	≥2	1146	22%	20%	24%	835	22%	18%	26%	311	23%	17%	29%
III	***0***	1075	17%	15%	19%	410	22%	18%	26%	665	14%	12%	16%
	1	1574	26%	24%	28%	627	29%	25%	33%	947	24%	22%	26%
	≥2	2563	44%	42%	46%	987	45%	41%	49%	1576	44%	42%	46%
Stage II (pN0)													
pT3	***0***	2862	9%	7%	11%	2743	9%	7%	11%	119	13%	7%	19%
	1	1834	11%	9%	13%	1641	10%	8%	12%	193	12%	8%	16%
	≥2	637	19%	15%	23%	533	19%	15%	23%	104	15%	7%	23%
pT4	***0***	313	16%	12%	20%	195	15%	9%	21%	118	16%	8%	24%
	1	302	24%	18%	30%	190	24%	18%	30%	112	25%	17%	33%
	≥2	207	31%	23%	39%	112	31%	21%	41%	95	32%	22%	42%
Stage III (pN1)													
pT1-3	***0***	1075	17%	15%	19%	410	22%	18%	26%	665	14%	12%	16%
	1	1020	22%	20%	24%	456	24%	20%	28%	564	21%	17%	25%
	≥2	557	27%	23%	31%	282	31%	25%	37%	275	24%	18%	30%
pT4	***0***	172	31%	23%	39%	65	35%	21%	49%	107	28%	18%	38%
	1	236	34%	28%	40%	101	36%	24%	48%	135	33%	25%	41%
	≥2	254	49%	43%	55%	103	52%	40%	64%	151	47%	39%	55%
Stage III (pN2)													
pT1-3	***0***	382	34%	28%	40%	106	44%	34%	54%	276	30%	24%	36%
	1	466	38%	34%	42%	156	44%	36%	52%	310	35%	29%	41%
	≥2	495	55%	51%	59%	171	59%	51%	67%	324	54%	48%	60%
pT4	***0***	63	50%	36%	64%	15	52%	23%	81%	48	50%	36%	64%
	1	166	46%	38%	54%	42	41%	23%	59%	124	47%	37%	57%
	≥2	326	64%	58%	70%	117	58%	48%	68%	209	66%	60%	72%

[a] RF defined by NCCN were pT4, pN2, emergency surgery, high-grade malignancy, vascular or perineural invasion, less than 12 sampled lymph nodes.

[b] 95% confidence interval (CI) of estimates.

Table 3: Univariable Cox proportional hazards model for TTR and OS for major factors

		TTR	95% CI [b]			OS	95% CI [b]		
		HR [a]	Lower	Upper	p	HR[a]	Lower	Upper	p
Sex	***Male***	1.0	(Ref)						
	Female	0.9	0.8	0.9	0.001	0.9	0.8	0.9	0.000
Side	***Right***	1.0	(Ref)						
	Left	1.1	1.0	1.1	0.191	0.8	0.8	0.9	0.000
Surgery	***Elective***	1.0	(Ref)						
	Emergency	2.4	2.2	2.7	0.000	1.9	1.8	2.0	0.000
pT	***pT1***	1.0	(Ref)			1.0	(Ref)		
	pT2	1.9	1.4	2.7	0.000	1.4	1.2	1.6	0.000
	pT3 all	4.8	3.5	6.4	0.000	1.7	1.5	1.9	0.000
	pT3ab	3.3	2.4	4.5	0.000	1.5	1.3	1.7	0.000
	pT3cd	7.0	5.1	9.5	0.000	1.9	1.7	2.2	0.000
	pT3 unknown	5.0	3.7	6.8	0.000	1.8	1.6	2.1	0.000
	pT4 all	11.2	8.2	15.2	0.000	3.0	2.7	3.5	0.000
	pT4a	12.5	9.0	17.4	0.000	3.5	2.9	4.1	0.000
	pT4b	9.3	6.3	13.6	0.000	3.0	2.4	3.7	0.000
	pT4 unknown	11.1	8.1	15.2	0.000	2.9	2.6	3.4	0.000
	Missing	4.0	1.9	8.6	0.000	2.2	1.4	3.3	0.000
pN	***pN0***	1.0	(Ref)			1.0	(Ref)		
	pN1	2.6	2.4	2.9	0.000	1.4	1.3	1.4	0.000
	pN2a	5.0	4.4	5.7	0.000	1.9	1.7	2.1	0.000
	pN2b	7.9	7.0	8.9	0.000	2.9	2.6	3.2	0.000
	Missing	0.6	0.3	0.9	0.019	0.8	0.6	1.0	0.039
Stage	***Stage I***	1.0	(Ref)						
	Stage II	2.6	2.2	3.2	0.000	1.3	1.2	1.4	0.000
	Stage III	8.0	6.6	9.7	0.000	1.9	1.8	2.1	0.000
Malignancy	***Low-grade***	1.0	(Ref)			1.0	(Ref)		
	High-grade	1.5	1.4	1.7	0.000	1.4	1.3	1.5	0.000
	Missing	0.9	0.7	1.1	0.174	1.2	1.0	1.3	0.012
Vascular	***No***	1.0	(Ref)						
invasion	***Yes***	3.1	2.8	3.4	0.000	1.8	1.7	2.0	0.000
	Missing	1.3	1.2	1.5	0.000	1.2	1.1	1.3	0.000
Perineural	***No***	1.0	(Ref)						
invasion	***Yes***	3.1	2.8	3.5	0.000	1.9	1.7	2.0	0.000
	Missing	1.3	1.2	1.4	0.000	1.2	1.1	1.2	0.000
Nodes	***Each investigated***	1.0	1.0	1.0	0.664	1.0	1.0	1.0	0.000
	Each positive	1.1	1.1	1.1	0.000	1.1	1.1	1.1	0.000
Adjuvant	***No***	1.0	(Ref)						
treatment	***Yes***	2.2	2.1	2.4	0.000	0.7	0.6	0.7	0.000
By stage	***Stage II, adjuvant***	1.6	1.3	1.9	0.000	0.5	0.4	0.6	0.000
	Stage III, adjuvant	0.9	0.8	1.0	0.004	0.3	0.3	0.4	0.000

[a] Unadjusted hazard ratio (HR) [b] 95% confidence interval (CI).

Table 4: Multivariable Cox proportional hazards model for TTR

		TTR	95% CI		
		HR [a]	**Lower**	**Upper**	**p**
Sex	***Male***	1.0	(Ref)		
	Female vs male	0.9	0.8	0.9	0.000
Surgery	***Elective***	1.0	(Ref)		
	Emergency	1.6	1.5	1.8	0.000
Pretherapeutic staging	***No staging***	1.0	(Ref)		
	Lung staged	1.0	0.8	1.2	0.885
	Liver staged	0.9	0.8	1.1	0.450
Ligature	***Central ligature***	1.0	(Ref)		
	Distal ligature	1.1	1.0	1.2	0.023
	Polypectomy patients [b]	0.2	0.0	1.2	0.072
	Missing	1.3	1.1	1.5	0.001
CRM [c]	***<3 mm***	1.0	(Ref)		
	3-10 mm	1.0	0.8	1.2	0.897
	>10 mm	0.9	0.8	1.1	0.377
	Missing	1.1	0.9	1.2	0.477
LRM [d]	***<50 mm***	1.0	(Ref)		
	50-90 mm	0.9	0.8	1.0	0.044
	>90 mm	0.9	0.8	1.1	0.309
	Missing	1.1	0.9	1.2	0.351
pT	***pT1***	1.0	(Ref)		
	pT2	1.6	1.1	2.3	0.011
	pT3ab	2.3	1.6	3.2	0.000
	pT3cd	3.3	2.4	4.7	0.000
	pT3 unknown	2.7	1.9	3.8	0.000
	pT4a	5.0	3.5	7.2	0.000
	pT4b	4.3	2.8	6.4	0.000
	pT4 unknown	4.8	3.4	6.7	0.000
	Missing	4.7	2.0	11.2	0.000
pN0	***pN0***	1.0	(Ref)		
	pN1	2.1	1.9	2.4	0.000
	pN2a	3.4	2.9	3.9	0.000
	pN2b	4.3	3.5	5.2	0.000
	Missing	1.5	0.8	2.7	0.249
Malignancy	***Low-grade***	1.0	(Ref)		
	High-grade	1.0	0.9	1.1	0.674
	Missing	0.9	0.7	1.1	0.160
Vascular invasion	***No***	1.0	(Ref)		
	Yes	1.5	1.3	1.6	0.000
	Missing	1.2	1.1	1.5	0.006
Perineural invasion	***No***	1.0	(Ref)		
	Yes	1.3	1.2	1.5	0.000
	Missing	1.0	0.9	1.2	0.856
Nodes	***Each positive***	1.0	1.0	1.0	0.004
Postoperative complications	***No***	1.0	(Ref)		
	Yes	1.1	1.0	1.2	0.021
	No	1.0	(Ref)		

Adjuvant treatment	***Yes***	0.8	0.7	0.9	0.000

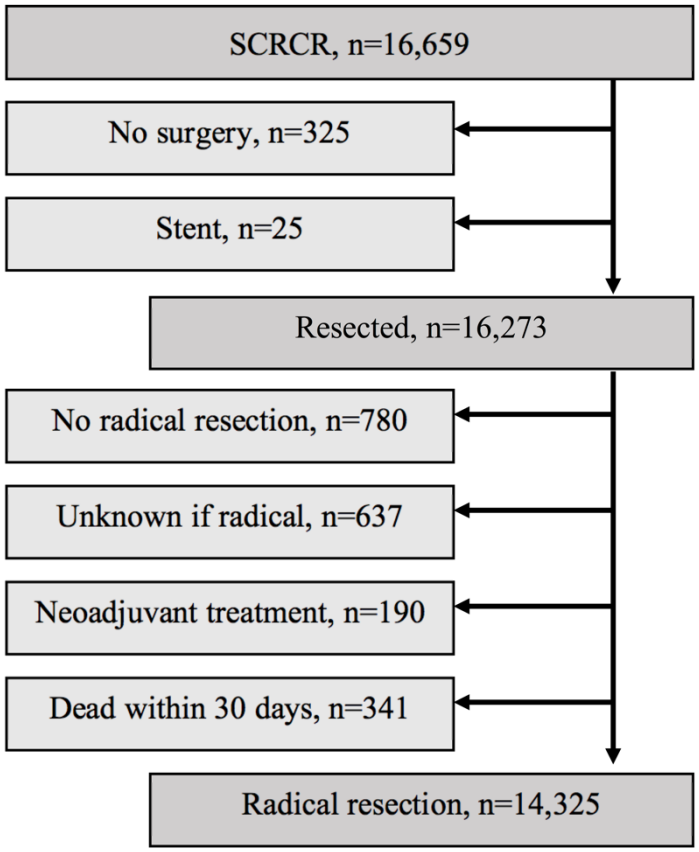
[a] Adjusted hazard ratio (HR)

[b] Patients who underwent endoscopic polypectomy

[c] CRM: Circumferential resection margin

[d] LRM: Longitudinal resection margin.

Figure 1*:* Flow chart of the cohort and selection of patients



Data from the SCRCR included all patients with stage I – III cancers diagnosed between 2007 and 2012. "No radical resection" was defined as non-radical surgery by the surgeon and tumor cells at the resection surface (R2) and "unclear/doubtful if radical" if the pathologist reported tumor cells at the resection surface (R1). Stent indicates that stenting was performed as a bridge to surgery.

Figure 2A: Kaplan Meier curve for TTR in stage II factored by the number of risk factors

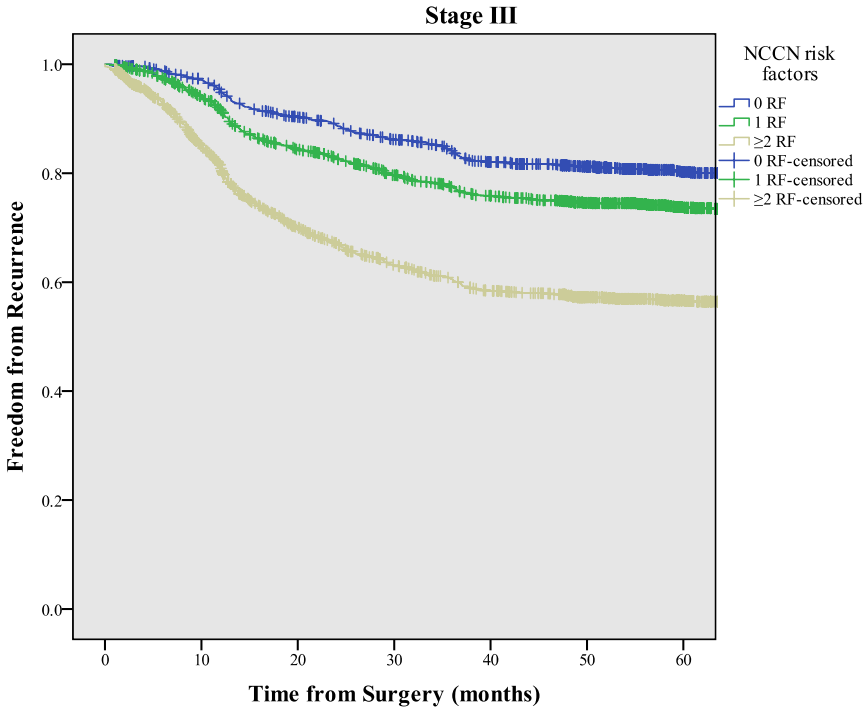
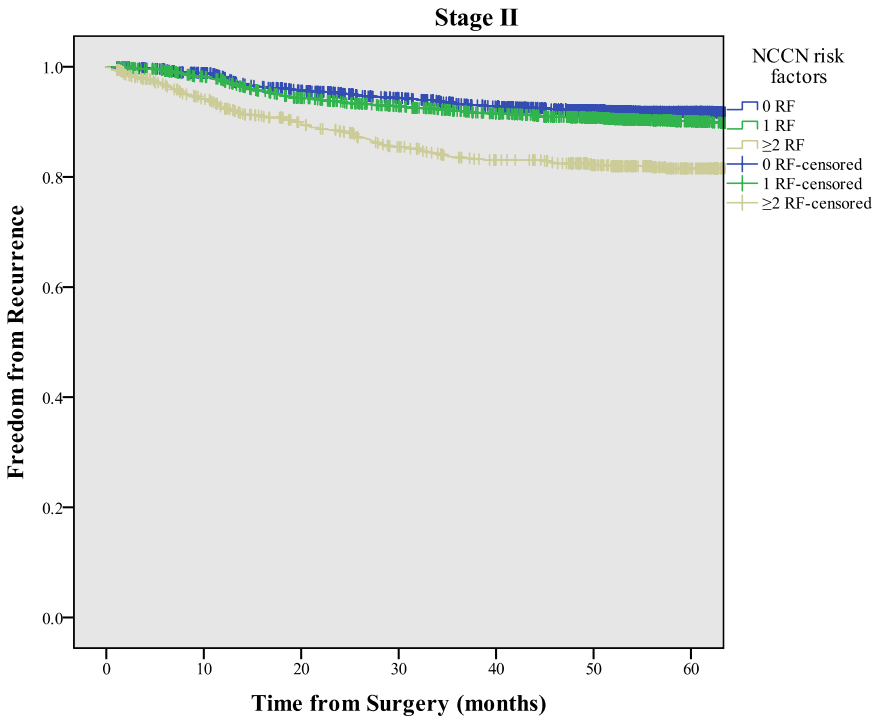


Figure 2B: Kaplan Meier curve for TTR in stage III factored by the number of risk factors



Risk factors were: emergency surgery, high-grade malignancy, vascular or perineural invasion, less than 12 sampled lymph nodes, and pT4 classification.

Supplementary tables and information

Supplementary Table 1: Parameters and distributions regarding recurrence and mortality for additional factors

[a] Proportions tested with Pearsons-$\chi 2$ test.

[b] Region: Location of patient surgery.

[c] BMI: Body mass index.

[d] American Society of Anesthesiologists' classification (ASA) rated by an anesthesiologist before surgery.

[e] Patients who underwent endoscopic polypectomy

[f] CRM: Circumferential resection margin

[g] LRM: Longitudinal resection margin.

Supplementary Table 2: Univariable Cox proportional hazards model for TTR and OS for additional factors

[a] Unadjusted hazard ratio (HR)

[b] 95% confidence interval (CI).

[c] Region: Location of patient surgery.

[d] Body mass index (BMI) calculated before surgery.

[e] American Society of Anesthesiologists' classification (ASA) rated by an anesthesiologist before surgery.

[f] Patients who underwent endoscopic polypectomy

[g] CRM: Circumferential resection margin

[h] LRM: Longitudinal resection margin.

Supplementary Table 3: Multivariable Cox proportional hazards model for OS

[a] Adjusted hazard ratio (HR)

[b] Region: Location of patient surgery.

[c] Body mass index (BMI) calculated before surgery.

[d] American Society of Anesthesiologists' classification (ASA) rated by an anesthesiologist before surgery.

[e] CRM: Circumferential resection margin,

[f] LRM: Longitudinal resection margin.

[g] 95% confidence interval (CI).

Supplementary Table 4: Changes in aspects of quality of care between 2007 and 2012

p-values for proportions tested with Pearsons-$\chi 2$ test.

[a] CRM: Circumferential resection margin

[b] LRM: Longitudinal resection margin.