Journal of Gastrointestinal Surgery (2019) 23:1884–1892
https://doi.org/10.1007/s11605-018-4054-9

ORIGINAL ARTICLE

# Do Stage I Colorectal Cancers with Lymphatic Invasion Require a Different Postoperative Approach?

Lieve G. J. Leijssen[1] · Anne M. Dinaux[1] · Hiroko Kinutake[1] · Liliana G. Bordeianou[1] · David L. Berger[1]

Received: 19 September 2018 / Accepted: 12 November 2018 / Published online: 3 December 2018


## Abstract

**Background** Although stage I colorectal cancer has an excellent prognosis after complete surgical resection, disease recurrence still occurs. This study aimed to assess prognostic risk factors in this early stage of disease.

**Methods** All non-neoadjuvantly treated stage I colon (CC) and rectal (RC) patients who underwent a surgical resection between 2004 and 2015 were identified. Clinicopathological differences and long-term oncological outcomes were compared.

**Results** CC patients ($n = 433$) were older and had more pre-existing comorbidities. RC patients ($n = 86$) were associated with more T2 tumors, venous invasion, and higher rates of 30-day morbidity. In multivariate analysis, lymphatic invasion was found to be an independent predictor for disease recurrence (OR 4.57, $P = 0.010$) and worse disease-free survival (HR 4.26, $P = 0.012$). This was particularly true for distant recurrence, with eight times higher hazard ratios when lymphatic invasion was present (HR 8.02, $P < 0.001$). T2 tumors were at risk, though no significant association was found (OR 3.86, $P = 0.051$; HR 3.61, $P = 0.065$, respectively).

**Conclusions** Lymphatic invasion was strongly associated with worse DFS, in particular distant recurrence. This subgroup of stage I patients might benefit from a more intensive follow-up and maybe should be considered for adjuvant therapy.

**Keywords** Colorectal cancer · Early stage · Postoperative morbidity · Disease recurrence · Risk factors

**Abbreviations**

| | |
|---|---|
| AJCC | American Joint Committee on Cancer |
| APR | Abdominoperineal resection |
| ASA | American Society of Anesthesiologists |
| BMI | Body mass index, kg/m$^2$ |
| CC | Colon cancer |
| CI | Confidence interval |
| DFS | Disease-free survival |
| DR | Distant recurrence |
| HR | Hazard ratio |
| LAR | Low anterior resection |
| LR | Local recurrence |
| LVI | Lymphovascular invasion |
| MSI | Microsatellite instability |
| OS | Overall survival |
| RC | Rectal cancer |

**Scientific meeting presentations** Poster of distinction at New England Surgical Society (September 9–11 2017, Bretton Woods, NH)

✉ David L. Berger
dberger@mgh.harvard.edu

[1] Department of General and Gastrointestinal Surgery, Massachusetts General Hospital, Harvard Medical School, 15 Parkman Street, Boston, MA 02114, USA

## Introduction

Colorectal cancer (CRC) has a profound impact on public health. In 2017, an estimated 135,430 new cases of large bowel cancer were diagnosed in the United States.[1] Due to screening programs, changing patterns in risk factors, and improvements in treatment, a declining trend in CRC incidence and mortality is noted over the last decades.[2] Nonetheless, CRC is still the third most commonly diagnosed cancer among men and women and approximately 50,260 patients died from colorectal cancer in 2017. The overall 5-year survival rate for patients diagnosed with CRC between 2006 and 2012 was 65%, slightly higher for rectal cancer (67% vs. 64%).[3] This rate is dependent upon many factors, but stage of disease at diagnosis remains one of the most important in oncological outcomes.

Approximately 39% of all CRC patients present with localized disease, including all cases where the cancer is found to be confined to the primary site. Surgical resection without neoadjuvant or adjuvant chemoradiation is still the gold standard for these patients, notwithstanding the increasing interest and improved techniques for less invasive procedures such as transanal excision in rectal cancer and endoscopic removal of colonic neoplasms over the last decades.[4,5] The estimated 5-year survival rate reaches 90% for this early-stage disease; thus, the prognosis is excellent. Nonetheless, disease recurrence rates are in the range of 5–17%.[6–8]

An established risk factor for disease recurrence in stage I disease is method of resection, particularly in rectal cancer since a local excision has become a more commonly used procedure. Other than that, however, not much is known about prognostic risk factors in this stage of colorectal cancer. Most of the studies which focus on poor outcomes in early-stage CRC either include stage I and II disease[9,10] or investigated predictors for lymph node metastasis[11–13] and are therefore less applicable to pT1-2N0 tumors. In addition, although colon and rectal cancers have a different tumor biology and require different treatments in more advanced stages, the recommendations for stage I disease are not different between the two. To further optimize prognosis, particularly with the current increase in less invasive procedures, it is essential to increase our knowledge of prognostic factors in early-stage disease. Therefore, the objective of this study is to examine risk-stratifying factors in stage I colorectal cancer and to assess differences between colon and rectal cancer patients.

## Materials and Methods

### Study Design and Patients

The study population consisted of all patients who underwent primary surgical treatment for stage I colon or rectal cancer at Massachusetts General Hospital between 2004 and 2015. All data was extracted from a prospectively maintained, IRB-approved database. Patient who received neoadjuvant treatment for stage II disease and downgraded to pathologic stage I were excluded ($n = 11$) as were patients who underwent a transanal excision ($n = 19$). The remaining 519 cases were included for subsequent analysis. Colon cancer (CC) was defined as a tumor located between the cecum and sigmoid. Rectal cancer (RC) included all tumors within 15 cm of the anal verge. Baseline characteristics, operative and postoperative details, pathology features, and long-term outcomes were reviewed. Surgical procedures were compared, including segmental colectomies, low anterior resection (LAR), and abdominoperineal resection (APR). Short-term outcomes included length of stay, rate of readmission, complications during and post-admission, and mortality within 30 days of surgery. Long-term outcomes included the rate of recurrence, both local and distant recurrence rates, as well as overall survival (OS) and disease-free survival (DFS). Local recurrence was defined as peri-anastomotic recurrence or regional nodal recurrence, while distant metastasis included other organs such as the liver, lung, peritoneum, bone, and brain. Data on long-term outcomes was updated periodically by reviewing patient's records and the Massachusetts General Hospital's cancer registry. All time to events was calculated from date of surgery.

### Statistical Analysis

All statistical analyses were performed using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Macintosh, Version 24.0. Armonk, NY: IBM Corp.). Differences in dichotomous variables were assessed using a chi-squared ($\chi^2$) test, and categorical variables are presented as the percentage of patients. Continuous variables are presented as the mean ± standard deviation (SD) or the median and interquartile range (IQR), according to the distribution (Kolmogorov-Smirnov and Shapiro-Wilk tests). Differences in continuous variables were analyzed using a Mann-Whitney $U$ test. Survival analyses were performed with Kaplan-Meier curves, using a log-rank test. Multiple logistic regression models were used to determine the association between disease recurrence, tumor location, and other clinicopathological variables. Significant explanatory univariate variables, as well as clinically important factors, were considered as potential covariates and were kept in the model if they improved the goodness of fit, according to Hosmer-Lemeshow purposeful variable selection method.[14] The results are reported as odds ratios (OR) with a 95% confidence interval (CI). Furthermore, we performed Cox proportional hazard models to assess the impact on time to disease recurrence, reported as hazard ratios (HR) with a 95% CI. All reported $P$ values are two sided, with $P \leq 0.05$ denoting statistical significance.

## Results

Between 2004 and 2015, 433 CC and 86 RC patients with stage I disease underwent a surgical resection at our institution. Median age was 66.3 years. Rectal cancer patients were significantly younger (67.3 vs. 59.7, $P = 0.001$). CC was associated with a higher ASA score ($P = 0.027$) and more urgent admissions (5.5% vs. 0.0%, $P = 0.025$). One third of the CC patients received surgical resection for a T2 tumor, while the majority of surgically treated RC patients had a T2 tumor (58.1%, $P < 0.001$). High-grade tumors were rarely seen and only present in CC tumors (6.8%, $P = 0.014$), whereas the prevalence of lymphovascular invasion (LVI), and in particular venous invasion, was significantly higher in RC tumors (11.3% vs. 33.7%, $P < 0.001$). Besides tumor location, LVI was found to be correlated with histological risk factors including pT2 tumors (OR

4.79, $P < 0.001$), poor differentiation (OR 2.86, $P = 0.010$), and perineural invasion (OR 3.34, $P = 0.046$). The prevalence of microsatellite instability was significantly different between tumor locations, with more MSI stable and low tumors in the rectal cancer cohort (27.0% vs. 46.5%, $P < 0.001$). Although the number of retrieved lymph nodes was comparable, more CC patients had less than 12 lymph nodes harvested (18.0% vs. 9.3%, $P = 0.047$) (Table 1).

## Intra- and Postoperative Outcomes

Table 2 demonstrates perioperative outcomes. The majority of patients underwent open surgery (CC 51.3% vs. RC 60.5%) explained by the length of the study. There was a remarkable shift towards laparoscopic surgery over the study period, with an average of 31.8% procedures done laparoscopically in the first half of the study and 65.3% in the latter. The procedures performed in the rectal group were low anterior resections (LAR, 89.0%) and abdominoperineal resections due to sphincter involvement (APR, 11.0%). Surgery for rectal cancer took significantly longer (124 vs. 194 min, $P < 0.001$), with no differences in intraoperative complications. RC patients experienced more complications during their initial admission (23.6% vs. 40.7%, $P = 0.001$) and had a higher readmission rate (7.2% vs. 15.1%, $P = 0.016$). The most common reasons for readmission were dehydration (36.4%), ileus (27.3%), and anastomotic leakage (18.2%). While the overall rates of anastomotic leak/intra-abdominal abscesses, surgical site infections, and urinary tract infections were only slightly higher, postoperative ileus occurred significantly more often in RC patients (10.9% vs. 20.9%, $P = 0.010$).

## Long-term Outcomes

Median follow-up duration at our institution was 51.4 months, which was shorter for RC patients (55.8 vs. 41.5 months, $P = 0.022$) (Table 3). Of all CC patients, 2.3% experienced cancer recurrence versus 4.7% of RC patients ($P = 0.221$). Median time to disease recurrence was 1 year later in CC (52.3 months vs. 39.8 months, $P = 0.015$). This was mainly explained by local

**Table 1** Baseline characteristics

| $n = 519$ | All patients $n = 519$ | Colon cancer $n = 433$ (83.4%) | Rectal cancer $n = 86$ (16.6%) | $P$ value |
|---|---|---|---|---|
| Age | 66.3 (56.2–75.8) | 67.3 (57.4–77.0) | 59.7 (51.6–72.3) | 0.001 |
| Male gender | 281 (54.1%) | 233 (53.8%) | 48 (55.8%) | 0.733 |
| BMI | 26.9 (23.4–31.2) | 27.1 (23.7–31.6) | 26.4 (22.6–30.1) | 0.085 |
| ASA | 2 (2–3) | 2 (2–3) | 2 (2–2) | 0.027 |
| IBD | 22 (4.2%) | 20 (4.6%) | 2 (2.3%) | 0.335 |
| Alcohol abuse | 35 (6.7%) | 30 (6.9%) | 5 (5.8%) | 0.707 |
| Nicotine dependence | 55 (10.6%) | 46 (10.6%) | 9 (10.5%) | 0.965 |
| Urgent admission | 24 (4.6%) | 24 (5.5%) | 0 (0.0%) | 0.025 |
| Family history CRC | 71 (13.7%) | 59 (13.6%) | 12 (14.0%) | 0.936 |
| History of cancer | 67 (12.9%) | 53 (12.2%) | 14 (16.3%) | 0.308 |
| Pathology features | | | | |
| T2 tumor | 209 (40.3%) | 159 (36.7%) | 50 (58.1%) | < 0.001 |
| High grade | 28 (5.6%) | 28 (6.8%) | 0 (0.0%) | 0.014 |
| LVI | 78 (15.0%) | 49 (11.3%) | 29 (33.7%) | < 0.001 |
| Lymphatic | 53 (10.2%) | 41 (9.5%) | 12 (14.0%) | 0.210 |
| Venous | 26 (5.0%) | 12 (2.8%) | 14 (16.3%) | < 0.001 |
| Perineural invasion | 11 (2.1%) | 8 (1.9%) | 3 (3.5%) | 0.336 |
| Microsatellite instability | | | | < 0.001 |
| MSI stable or low | 157 (30.3%) | 117 (27.0%) | 40 (46.5%) | |
| MSI high | 31 (6.0%) | 31 (7.2%) | 0 (0.0%) | |
| Unknown | 331 (63.8%) | 285 (65.8%) | 46 (53.5%) | |
| LN examined | 18 (14–24) | 18 (13–25) | 17 (15–23) | 0.592 |
| LN < 12 examined | 86 (16.6%) | 78 (18.0%) | 8 (9.3%) | 0.047 |
| Tumor size (cm) | 2.0 (0.0–3.5) | 2.0 (0.0–3.5) | 2.1 (0.0–15.0) | 0.066 |

Proportions are presented for categorical data, median with IQR for continuous data

*BMI*, body mass index (kg/m$^2$ ); *ASA*, American Society of Anesthesiologists; *IBD*, inflammatory bowel disease; *LVI*, lymphovascular invasion

**Table 2** Intra- and postoperative outcomes

| | All patients | Colon cancer | Rectal cancer | *P* value |
|---|---|---|---|---|
| Surgery | | | | |
| Operation duration (min) | 139 (80–190) | 124 (74–171) | 194 (144–237) | < 0.001 |
| Laparoscopic approach | 245 (47.2%) | 211 (48.7%) | 34 (39.5%) | 0.119 |
| Conversion to open surgery | 17 (3.3%) | 13 (3.0%) | 4 (4.7%) | 0.433 |
| Admission | | | | |
| Admission duration (days) | 4 (3–6) | 4 (3–6) | 5 (4–7) | 0.004 |
| Complication rate during admission | 137 (26.4%) | 102 (23.6%) | 35 (40.7%) | 0.001 |
| Complication rate total | 172 (33.1%) | 127 (29.3%) | 45 (52.3%) | < 0.001 |
| Ileus | 65 (12.5%) | 47 (10.9%) | 18 (20.9%) | 0.010 |
| Abscess/leak | 15 (2.9%) | 11 (2.5%) | 4 (4.7%) | 0.286 |
| Surgical site infection | 54 (10.4%) | 43 (9.9%) | 11 (12.8%) | 0.428 |
| Sepsis | 3 (0.6%) | 3 (0.7%) | 0 (0.0%) | 0.741 |
| Blood transfusion | 75 (14.5%) | 65 (15.0%) | 10 (11.6%) | 0.415 |
| ICU transfer | 14 (2.7%) | 9 (2.1%) | 5 (5.8%) | 0.051 |
| Pneumonia | 12 (2.3%) | 10 (2.3%) | 2 (2.3%) | 0.993 |
| Renal failure/insufficiency | 14 (2.7%) | 12 (2.8%) | 2 (2.3%) | 0.816 |
| Urinary tract infection | 23 (4.4%) | 17 (3.9%) | 6 (7.0%) | 0.209 |
| Readmission | 44 (8.5%) | 31 (7.2%) | 13 (15.1%) | 0.016 |
| Reoperation | 16 (3.1%) | 13 (3.0%) | 3 (3.5%) | 0.812 |
| Death | 3 (0.6%) | 2 (0.5%) | 1 (1.2%) | 0.434 |

Proportions are presented for categorical data, median with IQR for all continuous data

recurrence, which was earlier detected in RC (CC 55.8 months, RC 16.2 months, $P = 0.038$). With regard to survival, rates of overall mortality were higher in CC patients (21.5% vs. 11.6%, $P = 0.036$), whereas colorectal cancer mortality rates were scarce and comparable (2.3% vs. 0.0%, $P = 0.155$, respectively). Log-rank testing demonstrated a similar 5-year overall survival (CC 84.3% vs. RC 85.5%, $P = 0.242$) as well as 5-year disease-free survival (CC 97.1% vs. RC 94.0%, $P = 0.144$).

## Multivariate Analyses

Table 4 demonstrates the outcomes of the logistic regression model and the Cox proportional hazard model. In univariate analysis, the odds of developing disease recurrence were remarkably higher after open surgery, tumors ≥ 2 cm, T2 tumors, lymphatic invasion, and perineural invasion. Patients with colon cancer had lower odds of disease recurrence (OR 0.49, $P = 0.221$). After adjustment, while the odds were clinically higher for T2 tumors (OR 3.86, $P = 0.051$), only lymphatic invasion was found to be an independent predictor for disease recurrence (OR 4.57, $P = 0.010$). When looking at time to disease recurrence, the same variables were found to have higher hazard ratios. Perineural invasion was contributory in the multivariate Cox model, though only lymphatic invasion was significantly associated with worse disease-free survival (HR 4.26, $P = 0.012$).

## Distant and Local Recurrence

We analyzed the impact of various variables on time to distant and local recurrence separately. As demonstrated in Fig. 1, lymphatic invasion, T-stage, and tumor location were

**Table 3** Long-term oncological outcomes

| | All patients | Colon cancer | Rectal cancer | *P* value |
|---|---|---|---|---|
| Recurrence | 14 (2.7%) | 10 (2.3%) | 4 (4.7%) | 0.221 |
| Local | 4 (0.8%) | 2 (0.5%) | 2 (2.3%) | 0.071 |
| Distant | 11 (2.1%) | 8 (1.8%) | 3 (3.5%) | 0.335 |
| Follow-up duration (months) | 51.4 (285–90.1) | 55.8 (29.2–93.1) | 41.5 (22.6–76.0) | 0.022 |
| Disease-free survival (months) | 49.4 (27.4–86.7) | 52.3 (28.2–90.4) | 39.8 (17.7–74.1) | 0.015 |
| Deceased | 103 (19.8%) | 93 (21.5%) | 10 (11.6%) | 0.036 |
| Colorectal cancer mortality | 10 (1.9%) | 10 (2.3%) | 0 (0.0%) | 0.155 |

Proportions are presented for categorical data, median with IQR for all continuous data

**Table 4** Univariate and multivariate analyses of disease recurrence and disease-free survival

| | Disease recurrence* | | | | | |
|---|---|---|---|---|---|---|
| | Patients, No. | Events, No. | Univariate | | Multivariate | |
| | | | OR (95% CI) | *P* value | OR (95% CI) | *P* value |
| Colon cancer | 433 | 10 | 0.49 (0.15–1.58) | 0.221 | | |
| ASA III-IV | 165 | 5 | 1.63 (0.56–4.77) | 0.370 | | |
| Age ≥ 65 years | 278 | 7 | 0.86 (0.30–2.50) | 0.863 | | |
| Urgent admission | 24 | 0 | – | – | | |
| Male gender | 281 | 7 | 0.84 (0.29–2.44) | 0.752 | | |
| Alcohol abuse | 35 | 1 | 1.07 (0.14–8.39) | 0.952 | | |
| Nicotine dependence | 55 | 0 | – | – | | |
| Open approach | 274 | 10 | 2.28 (0.71–7.37) | 0.157 | | |
| Postoperative complication | 172 | 3 | 0.54 (0.15–1.97) | 0.345 | | |
| Tumor size ≥ 2 cm | 235 | 9 | 2.18 (0.66–7.18) | 0.190 | | |
| T2 tumor | 209 | 11 | 5.69 (1.57–20.63) | 0.003 | 3.86 (0.99–14.95) | 0.051 |
| High grade | 28 | 0 | – | – | | |
| Lymphatic invasion | 53 | 6 | 7.31 (2.43–21.96) | < 0.001 | 4.57 (1.44–14.54) | 0.010 |
| Venous invasion | 25 | 1 | 1.48 (0.19–11.74) | 0.711 | | |
| Perineural invasion | 11 | 1 | 3.80 (0.45–31.92) | 0.187 | | |
| LN ≥ 12 | 433 | 11 | 0.72 (0.20–2.64) | 0.620 | | |
| | | | Disease-free survival** | | | |
| | 1-year estimate | 5-year estimate | Univariate | | Multivariate | |
| | | | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Colon cancer | 99.7% | 97.1% | 0.43 (0.14–1.38) | 0.144 | | |
| ASA III-IV | 99.3% | 94.8% | 1.74 (0.60–5.01) | 0.300 | | |
| Age ≥ 65 years | 99.6% | 96.4% | 0.91 (0.32–2.60) | 0.862 | | |
| Male gender | 99.2% | 97.2% | 1.08 (0.64–1.82) | 0.785 | | |
| Alcohol abuse | 96.7% | 96.7% | 0.97 (0.35–2.68) | 0.952 | | |
| Open approach | 99.2% | 95.9% | 1.87 (0.58–5.98) | 0.285 | | |
| Postoperative complication | 99.3% | 97.7% | 0.55 (0.15–1.95) | 0.344 | | |
| Tumor size ≥ 2 cm | 99.0% | 95.2% | 2.29 (0.71–7.45) | 0.155 | | |
| T2 tumor | 98.4% | 93.8% | 5.56 (1.55–19.94) | 0.003 | 3.61 (0.92–14.09) | 0.065 |
| Lymphatic invasion | 95.6% | 83.6% | 7.14 (2.48–20.57) | < 0.001 | 4.26 (1.38–13.20) | 0.012 |
| Venous invasion | 95.8% | 95.8% | 1.83 (0.24–14.00) | 0.557 | | |
| Perineural invasion | 100% | 90.0% | 3.84 (0.50–29.41) | 0.163 | 3.60 (0.47–27.86) | 0.219 |
| LN ≥ 12 | 99.5% | 96.8% | 0.75 (0.21–2.69) | 0.656 | | |

*Variables included in the model: T2 stage, lymphatic invasion

**Variables included in the model: T2 stage, lymphatic invasion, perineural invasion

associated with either distant or local recurrence. Lymphatic invasion was strongly related to distant recurrence (HR 8.02, 95% CI 2.45–26.29, $P < 0.001$), as were T2 tumors (HR 6.77, 95% CI 1.46–31.35, $P = 0.005$). Although hazard ratios for local recurrence were higher in patients with lymphatic invasion, the difference was not significant (HR 3.09, 95% CI 0.32–29.68, $P = 0.304$). The only factor associated with local recurrence was rectal cancer (HR 6.14, 95% CI 0.86–43.70, $P = 0.038$). Variables including surgical approach, tumor size, and other histopathologic features (venous invasion, perineural invasion, MSI, poor differentiation) were not associated with either one of the recurrence patterns.

## Discussion

Over the last decades, the incidence and mortality rates of colorectal cancer have decreased in Western countries.[15] The reason for this decline is multifactorial and reflects benefits of early detection through screening programs, awareness of risk factors, and therapeutic improvements. As with almost all types of cancer, the earlier the diagnosis, the better the outcomes. However, cure is never guaranteed even in early-stage disease. Despite the favorable outcome for patients with stage I colorectal cancer, disease recurrence still occurs. In line with recent SEER cancer statistics

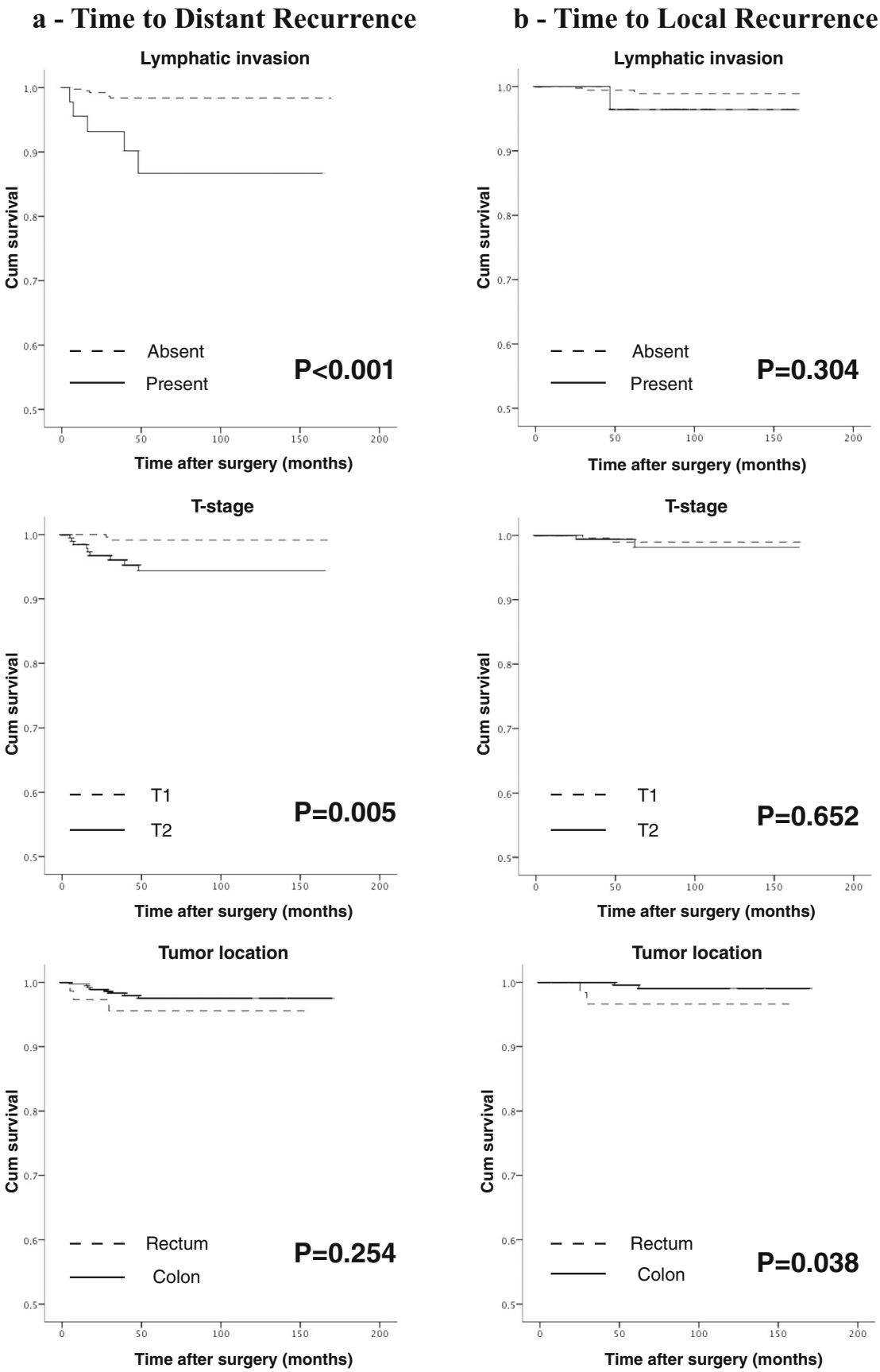


**Fig. 1** Kaplan-Meier curves for local and distant recurrence

outcomes, our study underlines the excellent prognosis, with an estimated 5-year overall survival of 84.3% for colon cancer and 85.5% for rectal cancer.[3] Yet, disease recurrence still occurred in 2.3% of all colon cancer patients and in twice as many as rectal cancer patients (4.7%). The corresponding 5-year disease-free survival was 97.1% and 94.0%, respectively. After adjustment, lymphatic invasion was found to be an independent predictor for worse disease-free survival. The prognostic impact of T2 tumors was present, with higher hazard ratios, though not significant.

The impact of depth of tumor invasion in lymph node–negative disease is better understood in rectal cancer than in colon cancer.[6,16] The increase over the last decade in local excisions for T1-T2 rectal cancer and subsequently the need to stratify risk factors for poor outcomes in early-stage rectal cancer have certainly contributed to that. As a result, the current NCCN, ESMO, and Japanese guidelines for stage I rectal cancer are based more on facts than assumptions.[4,5,17,18] When pathology demonstrates either a T2 tumor or other high-risk features including deep submucosal invasion (> 1 mm), positive margins, poorly differentiated tumors, and lymphovascular invasion, a transabdominal resection or adjuvant chemoradiation is required after a transanal excision. Considering colon cancer, one could presume that the risk factors applicable to stage I rectal cancer are valid for colon cancer as well, but definitive knowledge is lacking. Little is written about pT1-2N0 colon cancers, since previous studies either included all node-negative patients (pT1-pT4)[9,10] or investigated predictors for lymph node metastasis.[11–13] Additionally, the need to subdivide high- and low-risk stage I colon cancer patients has been less mandatory considering surgery as the gold standard associated with an excellent overall prognosis. The incremental benefit of postoperative treatment in lymph node–negative colorectal cancer in general is small, and most likely even smaller for T1-T2 tumors. Considering the risk of overtreatment and the associated morbidity of postoperative chemotherapy, indiscriminate use of postoperative treatment in localized CRC is definitely not recommended. However, assessing high-risk features in early-stage CRC might help to determine which patients would benefit from adjuvant therapy. Unfortunately, other than requirements after a local excision, recommendations for pT2 tumors with poor histology after a complete surgical resection remain unclear and data concerning stage I colon cancer in general is deficient.

For stage I colorectal cancer, the cause of disease recurrence is either undetectable local residual of the tumor or the presence of micrometastasis. Okabe et al. demonstrated already a decade ago the association between LVI and micrometastasis in patients with N0 disease in colorectal cancer.[19] Moreover, multiple studies reported histologic predictors for lymph node metastasis, including lymphovascular invasion.[20,21] In addition to that, a recent prospective multicenter trial concluded that LVI, along with high tumor grade, was correlated with occult nodal metastases in patients with colon cancer extended to the muscularis propria or beyond.[22] Along with T2 tumors, LVI is one of the histologic risk factors for which a local excision is contraindicated according to current guidelines. However, recommendations for LVI-positive T1 or T2 tumors after surgical resection remain unclear and do not differ from those for LVI-negative tumors as only surveillance is required in both groups, starting 1 year after surgery. In addition to previous studies, our study underlined the impact of lymphovascular invasion on surgically treated lymph node–negative T1 and T2 tumors as the presence of LVI was even stronger related to disease recurrence than pathologic T-stage. Moreover, an important difference between lymphatic and vascular invasion was demonstrated since only the first was found to be associated with worse outcomes. Tumors with lymphatic invasion carried over fourfold higher hazard ratios of disease-free survival (HR 4.26, $P = 0.012$), and lymphatic invasion was even more strongly associated with time to distant recurrence (HR 8.02, $P < 0.001$). Moreover, LVI in general was associated with other high-risk features in stage I disease, including pT2 tumors, high-grade tumors, and perineural invasion. Of all patients whom developed distant recurrence, 45.5% had LVI-positive tumors. This number was even more remarkable in rectal cancer (66.7%), and especially true for liver metastasis since all rectal cancer patients who were diagnosed with liver metastasis during their follow-up were LVI positive.

Besides the pathological risk factors found in our study, a number of differences between colon and rectal cancers were assessed. Previous studies elaborated on this distinction[23–25] which have led to modifications in treatment patterns and a more targeted disease management.[4,5] Considering stage I CRC, guidelines are not different and additional treatment in general after surgery is not given. Our study demonstrated a significant difference in the distribution of histopathologic factors, including more T2 tumors, LVI, and MSI stable or low tumors in rectal cancer patients. Nevertheless, tumor location was only associated with local recurrence. The fact that the incidence of venous invasion and not lymphatic invasion was higher might be a reasonable explanation for the comparable disease-free survival. Furthermore, we included only patients who underwent a surgical resection, which have led to a relatively higher number of T2 tumors in the rectal cohorts, since most T1 tumors were approached by a local excision. Incorporating those findings, we might conclude that guidelines for colon and rectal cancers do not need to be different in this early stage of disease.

Despite the existing controversy as to whether endoscopic removal of malignant colorectal polyps is feasible and as safe as the standard surgical approach,[26–28] it is clear that endoscopic removal for early-stage colonic

neoplasms has gained a lot of interest over the last years. As colonoscopic devices and techniques continue to improve, an increase in non-surgical treatment is expected, in both colon cancer and rectal cancer. Additionally, an increase in early-stage colorectal cancer is estimated due to colorectal screening. All of this increases the need to identify high-risk patients in this stage of disease. To our knowledge, this is one of the first studies that included only patients with stage I colon and rectal cancers and found a significant impact of lymphatic invasion in both tumor locations. Nevertheless, this study has several limitations. Although our database was prospectively maintained, potential biases inherent to our retrospective design apply to our study. Despite the noteworthy number of patients whom were referred to our hospital, possibly because of a relatively high comorbidity rate or difficulty of the surgical approach, the recurrence rate was lower compared to previous studies. The fact that we excluded all local excisions might have contributed to this relatively low recurrence rate. With regard to the low incidence of disease recurrence, we could only adjust for strongly associated univariate variables to minimize potential bias. Moreover, rates of disease-specific survival were too low to perform Cox proportional hazard models to assess independent factors associated with colorectal cancer mortality. Nonetheless, the main strength of the current study is the comparison between only stage I colon and rectal cancer patients, who underwent surgery in one single center during the same time frame.

In conclusion, although disease recurrence is uncommon in stage I colorectal cancer, it occurs. Lymphatic invasion is an independent predictor for worse disease-free survival and, in particular, strongly associated with distant recurrence. Therefore, we should be aware of potential worse outcomes in patients with lymphatic invasion in T1-T2 lymph node–negative colorectal tumors. The question now remains as to whether T2 and even T1 patients who have lymphatic invasion should receive routine oncologic follow-up or even adjuvant chemotherapy considering the risks of overtreatment and the marginal benefit in lymph node–negative colorectal cancer in general.[29]

**Authors' Contribution** All authors have contributed to this manuscript in the following way: substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of the data. Furthermore, all authors drafted or revised the manuscript critically for important intellectual content. All authors approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

## References


1. Siegel RL, Miller KD, Stacey A. Colorectal Cancer Statistics, 2017. CA Cancer J Clin. 2017;67:177–193
2. Edwards BK, Ward E, Kohler BA, Eheman C, Zauber AG, Anderson RN, Jemal A, Schymura MJ, Lansdorp-Vogelaar I, Seeff LC, van Ballegooijen M, Goede SL, Ries LA. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer 2010;116:544–573
3. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975- 2013. Bethesda, MD: National Cancer Institute; 2016
4. National Comprehensive Cancer Network. Colon Cancer (Version 2.2016).
5. National Comprehensive Cancer Network. Rectal Cancer (Version 2.2016).
6. Patel SA, Chen YH, Hornick JL, Catalano P, Nowak JA, Zukerberg LR, Bleday R, Shellito PC, Hong TS, Mamon HJ. Early-stage rectal cancer: clinical and pathologic prognostic markers of time to local recurrence and overall survival after resection. Dis Colon Rectum 2014;57:449–459
7. Bouvier AM, Launoy G, Bouvier V, Rollot F, Manfredi S, Faivre J, Cottet V, Jooste V. Incidence and patterns of late recurrences in colon cancer patients. Int J Cancer 2015;137:2133–2138
8. Bertelsen CA, Neuenschwander AU, Jansen JE, Wilhelmsen M, Kirkegaard-Klitbo A, Tenma JR, Bols B, Ingeholm P, Rasmussen LA, Jepsen LV, Iversen ER, Kristensen B, Gögenur I; Danish Colorectal Cancer Group. Disease-free survival after complete mesocolic excision compared with conventional colon cancer surgery: a retrospective, population-based study. The Lancet Oncology 2015;16:161–168
9. Mroczkowski P, Schmidt U, Sahm M, Gastinger I, Lippert H, Kube R. Prognostic factors assessed for 15,096 patients with colon cancer in stages I and II. World J Surg 2010;36:1693–1698
10. Young PE, Womeldorph CM, Johnson EK, Maykel JA, Brucher B, Stojadinovic A, Avital I, Nissen A, Steele SR. Early detection of colorectal cancer recurrence in patients undergoing surgery with curative intent: current status and challenges. J Cancer 2014;5:262–271
11. Kawachi H, Eishi Y, Ueno H, Nemoto T, Fujimori T, Iwashita A, Ajioka Y, Ochiai A, Ishiguro S, Shimoda T, Mochizuki H, Kato Y, Watanabe H, Koike M, Sugihara K. A three-tier classification system based on the depth of submucosal invasion and budding/sprouting can improve the treatment strategy for T1 colorectal cancer: a retrospective multicenter study. Mod Pathol 2015;28:872–879
12. Bosch SL, Teerenstra S, de Wilt JH, Cunningham C, Nagtegaal IDl. Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. Endoscopy 2013;45:827–834
13. Huh JW, Kim HR, Kim YJ. Lymphovascular or perineural invasion may predict lymph node metastasis in patients with T1 and T2 colorectal cancer. J Gastrointest Surg 2010;14:1074–1080
14. Lemeshow S, Hosmer DW Jr. A review of goodness of fit statistics for use in the development of logistic regression models. Am J Epidemiol 1982;115:92–106
15. Center MM, Jemal A, Smith RA, Ward E. Worldwide variations in colorectal cancer. CA Cancer J Clin 2009;59:366–378
16. Veereman G, Vlayen J, Robays J, Fairon N, Stordeur S, Rolfo C, Bielen D, Bols A, Demetter P, D'hoore A, Haustermans K, Hendlisz A, Lemmers A, Leonard D, Penninckx F, Van Cutsem E, Peeters M. Systematic review and meta-analysis of local

resection or transanal endoscopic microsurgery versus radical resection in stage I rectal cancer: A real standard? Crit Rev Oncol Hematol 2017;114:43–52
17. Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandalà M, Cervantes A, Arnold D; ESMO Guidelines Working Group. Early colon cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24:vi64–vi72
18. Watanabe T, Muro K, Ajioka Y, Hashiguchi Y, Ito Y, Saito Y, Hamaguchi T, Ishida H, Ishiguro M, Ishihara S, Kanemitsu Y, Kawano H, Kinugasa Y, Kokudo N, Murofushi K, Nakajima T, Oka S, Sakai Y, Tsuji A, Uehara K, Ueno H, Yamazaki K, Yoshida M, Yoshino T, Boku N, Fujimori T, Itabashi M, Koinuma N, Morita T, Nishimura G, Sakata Y, Shimada Y, Takahashi K, Tanaka S, Tsuruta O, Yamaguchi T, Yamaguchi N, Tanaka T, Kotake K, Sugihara K; Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. Int J Clin Oncol 2018;23:1–34
19. Okabe S, Shia J, Nash G, Wong WD, Guillem JG, Weiser MR, Temple L, Sugihara K, Paty PB. Lymph node metastasis in T1 adenocarcinoma of the colon and rectum. J Gastrointest Surg, 2004;8:1032–1039
20. Nascimbeni R, Burgart LJ, Nivatvongs S, Larson DR. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. Dis Colon Rectum 2002;45:200–206
21. Chok KS, Law WL. Prognostic factors affecting survival and recurrence of patients with pT1 and pT2 colorectal cancer. World J Surg 2007;31:1485–1490
22. Wasif N, Faries MB, Saha S, Turner RR, Wiese D, McCarter MD, Shen P, Stojadinovic A, Bilchik AJ. Predictors of occult nodal metastasis in colon cancer: results from a prospective multicenter trial. Surgery 2010;147:352–357
23. Wei EK, Giovannucci E, Wu K, Rosner B, Fuchs CS, Willett WC, Colditz GA. Comparison of risk factors for colon and rectal cancer. Int J Cancer 2004;108:433–442
24. van der Sijp MP, Bastiaannet E, Mesker WE, van der Geest LG, Breugom AJ, Steup WH, Marinelli AW, Tseng LN, Tollenaar RA, van de Velde CJ, Dekker JW. Differences between colon and rectal cancer in complications, short-term survival and recurrences. Int J Colorectal Dis 2016;31:1683–1691
25. Tamas K, Walenkamp AME, de Vries EG, van Vugt MA, Beets-Tan RG, van Etten B, de Groot DJ, Hospers GA. Rectal and colon cancer: Not just a different anatomic site. Cancer Treat Rev 2015;41:671–679
26. Backes Y, de Vos Tot Nederveen Cappel WH, van Bergeijk J, Ter Borg F, Schwartz MP, Spanier BWM, Geesing JMJ, Kessels K, Kerkhof M, Groen JN, Wolfhagen FHJ, Seerden TCJ, van Lelyveld N, Offerhaus GJA, Siersema PD, Lacle MM, Moons LMG. Risk for incomplete resection after macroscopic radical endoscopic resection of T1 colorectal cancer: a multicenter cohort study. Am J Gastroenterol. 2017;112:785–796
27. Seitz U, Bohnacker S, Seewald S, Thonke F, Brand B, Braiutigam T, Soehendra N. Is endoscopic polypectomy an adequate therapy for malignant colorectal polyps? Presentation of 114 patients and review of the literature. Dis Colon Rectum 2004;47:1789–1797
28. Yoshii S, Nojima M, Nosho K, Omori S, Kusumi T, Okuda H, Tsukagoshi H, Fujita M, Yamamoto H, Hosokawa M. Factors Associated With Risk for Colorectal Cancer Recurrence After Endoscopic Resection of T1 Tumors. Clin Gastroenterol Hepatol 2014;12:292–302
29. Quasar Collaborative Group, Gray R, Barnwell J, McConkey C, Hills RK, Williams NS, Kerr DJ. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet 2007;370:2020–2029