

ORIGINAL ARTICLE

Lymphovascular and perineural invasion in stage II rectal cancer: a report from the Swedish colorectal cancer registry

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ABSTRACT

Background: Adjuvant chemotherapy for stage II and III rectal cancer patients is a matter of discussion. The aim of the present study was to evaluate the prognostic value of lymphovascular (LVI) and perineural (PNI) invasion in stage II rectal cancer on a national level.

Materials and methods: Clinico-pathological factors associated with disease-free survival (DFS) and time to recurrence in stage II rectal cancer patients were analyzed from patient data registered in the Swedish Colorectal Cancer Registry between 2006 and 2012.

Results: Of 2649 patients with TNM stage II disease, 1395 (53%) received preoperative radiotherapy and 456 (17%) preoperative chemoradiotherapy. LVI and PNI were detected in 387 (15%) and 269 (10%) patients, respectively. Adjuvant chemotherapy was planned in 14%, but more often if LVI or PNI was detected (25% and 31%, respectively, $p < .001$ for both). The three-year DFS and time to recurrence were 78% and 17%, respectively. Both LVI and PNI indicated worse outcome. In patients not receiving postoperative chemotherapy, the risks of recurrence after three years were 20% if LVI was seen and 22% if PNI was detected ($p < .001$ for both). In the absence of LVI and PNI, it was 13% and 12%, respectively. In a multivariate Cox regression analysis, patients with LVI (hazard ratio 1.44, 95% CI 1.09–1.90; $p = .011$) and PNI (hazard ratio 1.80, 95% CI 1.34–2.43, $p < .001$) had significantly increased risks of recurrence.

Conclusions: Stage II rectal cancer patients with LVI and PNI have an increased risk of recurrence which emphasizes the need to properly evaluate the role of adjuvant chemotherapy particularly in these subgroups.

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Introduction

Colorectal cancer (CRC) is the third most common cancer in both genders and the second most common cause of cancer death in Western countries. Approximately one third of CRCs are located in the rectum [1]. During recent decades, much emphasis has been put on specimen-oriented surgery [2,3], and a meticulous pathological examination [3,4] to correctly stage CRC patients in order to select those who would benefit from adjuvant chemotherapy. Magnetic resonance imaging (MRI) provides the basis for decisions on preoperative radiotherapy (RT) or chemoradiotherapy (CRT) in rectal cancer patients and has added to the therapeutic complexity [5].

Even though adjuvant chemotherapy is an established part of routine treatment in stage III and high risk stage II colonic cancer, its role in stage II with high-risk features and stage III rectal cancer is not as accepted [6–11]. There exists no standard definition of high-risk features for stage II rectal cancer patients but, in a similar manner to colonic cancer, pathological features such as perforation, low tumor differentiation, serosal extension, venous-, lymphatic- or perineural invasion (PNI), low number of examined lymph nodes have

been associated with a poor prognosis and these patients may thus have at least potentially a greater benefit from adjuvant chemotherapy [6,12,13]. According to ESMO guidelines (2013), adjuvant chemotherapy can be given in high-risk stage II (and stage III) rectal cancer even if the level of evidence is low [1]. In most studies reporting on lymphovascular invasion (LVI), both colonic and rectal cancer patients are included and, in the majority of the studies, the reported number of patients with LVI is low [14–18].

The aim of the present study was to evaluate the role of LVI and PNI in time to recurrence and disease-free survival (DFS) in stage II rectal cancer on a national level.

Materials and methods

Sweden has approximately 9 million inhabitants. All hospitals treating CRC deliver clinical, surgical, pathological and follow-up data to the Swedish Colorectal Cancer Registry (SCRCR), which has a coverage of more than 98% of diagnosed patients. A comprehensive summary of the Swedish Rectal Cancer Registry (SRRCR) has previously been reported [19].

Briefly, data are collected prospectively and include patient characteristics, preoperative evaluation, surgical details, histopathological findings and follow-up data. The registry is continuously validated and updated [19,20].

The staging of tumors was based on the international classification for malignant tumors (TNM) from the American Joint Committee on Cancer (AJCC), seventh edition. Vascular and PNI are two variables in the pathological report that have been reported during the entire study period. There has not been any distinction between LVI/venous invasion, or mural/extramural venous invasion; all have been registered as vascular invasion. Therefore, both features are referred to as LVI. The pathology guidelines did not recommend any specific immunohistochemical analysis of LVI, venous invasion or PNI.

The Swedish oncological guidelines published in 2008 and valid during the study period recommended participation in ongoing studies (i.e. PROCTOR/SCRIPT [21]) and did not recommend adjuvant chemotherapy in stage II or III rectal cancer patients.

Between 2006 and 2012, 8463 patients with rectal cancer (defined as a tumor within 15 cm from the anal verge) with stage I–III disease underwent a bowel resection. The study population comprised the 2701 bowel-resected rectal cancer patients with stage II tumors (T3/4N0M0) that were operated with a curative intent, i.e. an R0 resection was anticipated and with no signs of distant metastases. Fifty-two patients with complete pathological tumor response after preoperative CRT were excluded from further analysis. A local recurrence was defined in the registry as a pelvic recurrence situated below the level of sacral promontory irrespective of distant metastases. As not all patients planned for postoperative chemotherapy actually initiated and received the treatment, the term ‘considered for’ postoperative or adjuvant chemotherapy has been used.

DFS was defined as the time from the date of surgery to local recurrence and/or metastases or death irrespective of cause. Time to tumor recurrence (TTR) was defined as the time from the date of surgery to the date of local or distant recurrence. Deaths were censored observations in the analysis of TTR.

The dates of death were available in all cases and were acquired from the Swedish Death Registry. The study was approved by The Regional Ethics Review Board in Uppsala and followed the Declaration of Helsinki (Dnr 2015/038).

Statistical analyses

The data were analyzed using IBM SPSS Statistics, version 22 (Chicago, IL). A p-value of <.05 was considered statistically significant. The Kaplan–Meier estimate was used to calculate DFS rates and TTR. Differences between groups in Kaplan–Meier were tested using the log rank test. Univariate and multivariate Cox regression models were applied to identify factors affecting DFS and TTR. The multivariate Cox regression analysis was performed as a stepwise regression including all predictive variables in the univariate analyses, followed by an analysis including only statistically significant

variables. The variables which remained significant in the final analyses are presented. To avoid small sample sizes, the American Society of Anesthesiologists (ASA) score was recoded into dichotomous variables (ASA1 + 2 vs. ASA3 + 4). Age was categorized as <60, 61–69, 70–79, >80 years, examined number of lymph nodes as 0–11, 12–21 and >22 and tumor distance to anal verge was categorized as 0–5, 6–10 and 11–15 cm in the Cox models.

Results

The clinical, surgical and histopathological characteristics of rectal cancer patients operated with bowel resection with a curative intent are summarized in Table 1. Staging MRI was performed in 2625 (97%) patients. The pre-therapeutic MRI staging defined cT4 tumors in 544 (20%) patients and metastatic lymph nodes in 925 (34%) patients. In total, 1395 (53%) patients received preoperative RT and 456 (17%) preoperative CRT. When concomitant chemotherapy was not administered, the greater majority of patients underwent short-course RT (5 Gy × 5 in one week) followed by immediate surgery. The radiation dose delivered together with chemotherapy (usually capecitabine) during the study period amounted to approximately 50 Gy in 25–28 fractions in 5–6 weeks. In patients with a T4 lesion on MRI, the frequency of preoperative CRT was 55%.

Table 1. Clinical, surgical and histopathological characteristics of stage II patients resected for rectal cancer in Sweden between 2006 and 2012. Patients with lymphovascular invasion and perineural invasion are depicted.

	All patients (n = 2649)	LVI (n = 387)	PNI (n = 269)
Age (years) ^a	70 (14–98)	69 (31–95)	68 (34–93)
Gender			
Male	1644 (62)	236 (61)	171 (64)
Female	1005 (38)	151 (39)	98 (36)
Distance to anal verge (cm) ^a	9 (0–15)	9 (0–15)	8 (0–15)
ASA score			
1	480 (18)	65 (17)	54 (20)
2	1478 (56)	213 (55)	147 (55)
3	600 (23)	105 (27)	65 (24)
4	30 (1)	1 (0)	1 (0)
Missing	61 (2)	3 (1)	2 (1)
Preoperative RT	1395 (53)	223 (59)	165 (61)
Preoperative CRT	456 (17)	48 (12)	49 (18)
Bowel resection			
Anterior resection	1384 (52)	212 (55)	110 (41)
Abdominoperineal excision	879 (33)	128 (33)	114 (42)
Hartmann's operation	386 (15)	47 (12)	45 (17)
Intraoperative bowel perforation	142 (5)	18 (5)	19 (7)
Emergency surgical resection	31 (1)	6 (2)	2 (1)
Laparoscopic resection	219 (8)	23 (6)	21 (8)
Tumor differentiation			
Well/moderately differentiated	2160 (82)	292 (75)	196 (73)
Poorly differentiated	274 (10)	72 (19)	50 (19)
Missing	215 (8)	23 (6)	23 (8)
T stage			
pT3	2409 (89)	344 (89)	228 (85)
pT4	240 (9)	43 (11)	41 (15)
Examined number of lymph nodes ^a	15 (0–99)	15 (0–57)	14 (0–57)
Lymphovascular invasion	387 (15)	–	113 (42)
Perineural invasion	269 (10)	113 (29)	–
Mucinous cancer	313 (12)	26 (7)	27 (10)
Postoperative chemotherapy	378 (14)	98 (25)	82 (31)

^aValues are median (range). CRT: chemoradiotherapy; LVI: lymphovascular invasion; PNI: perineural invasion; RT: radiotherapy.

LVI and PNI were detected in 387 (15%) and 269 (10%) patients, respectively (Table 1). In 113 patients, both LVI and PNI were detected. There were no statistically significant differences between patients with and without LVI as regards age, gender, preoperative RT/RCT, resection type, and examined number of lymph nodes. The tumor distance from the anal verge was 9 cm in patients with LVI and 8 cm in patients with PNI, without any statistically significant difference but more patients with PNI were operated with an APE than those with LVI (42% vs. 33%, $p < .001$). In poorly differentiated tumors, LVI and PNI rates were 26% and 18% compared with 13% and 9% in well/moderately differentiated tumors ($p < .001$ for both).

In total, 14% of stage II rectal cancer patients were considered for postoperative chemotherapy. This proportion was higher in patients with LVI (25%) and PNI (31%) than in those without (13%), $p < .001$ for both categories. Of patients treated with CRT, 43% (189 patients) were considered for treatment with adjuvant chemotherapy.

Disease-free survival

The three-year DFS was 78%, irrespective of whether postoperative chemotherapy was considered or not, ($p = .651$ log rank test), (Figure 1). In univariate analyses, increased age, ASA score, lower situated tumor, intraoperative bowel perforation, APE or Hartmann's procedure were associated with poorer DFS. In addition, pathological variables such as pT4, mucinous tumors, low number of examined lymph nodes

and PNI were associated with a lower DFS; this was not the case for LVI (Table 2).

The factors affecting DFS in the multivariate Cox regression analysis, including all factors that were statistically significant ($p < .05$) in the univariate analyses, were age, ASA score, type of bowel resection, intraoperative bowel perforation, examined number of lymph nodes, T-stage and PNI (Table 3).

Time to recurrence

According to Kaplan–Meier, the three-year risk of recurrence was 17% in all patients. In patients who were not considered for postoperative chemotherapy, those with LVI (Figure 2) and PNI (Figure 3) had an increased risk of recurrence with a three-year risk of 20% versus 13% and 22% versus 12%, ($p < .001$ for both). In patients who were planned for postoperative chemotherapy, the risk of recurrence at three years was 25% versus 24% in patients with and without LVI ($p = .836$) and 42% versus 20%, ($p < .001$) in patients with and without PNI. In the univariate analyses, tumor distance to the anal verge, preoperative CRT, type of bowel resection, intraoperative bowel perforation, number of examined lymph nodes, T stage, tumor differentiation, mucinous tumor, PNI, LVI and whether adjuvant chemotherapy was given or not were all correlated to TTR (Table 3) and all were included in a multivariate Cox regression analysis, which demonstrated that preoperative CRT, APE and Hartmann's procedure, T stage, PNI and LVI were inversely correlated to TTR.

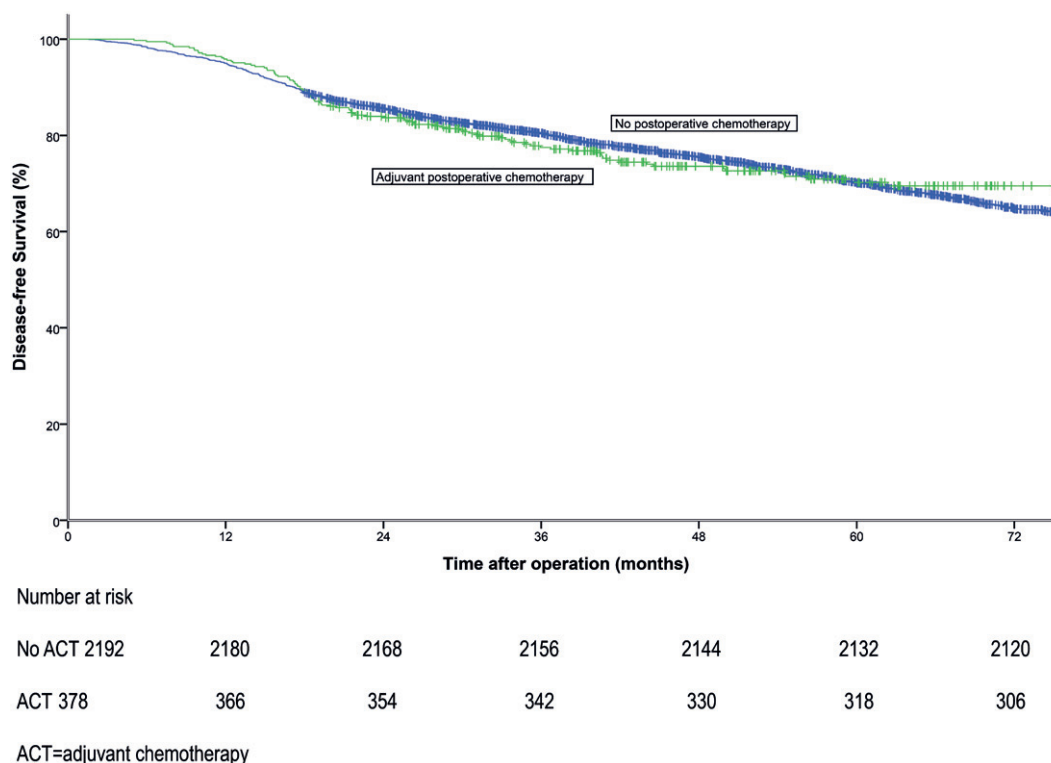


Figure 1. Kaplan–Meier analysis of disease-free survival in stage II rectal cancer patients in Sweden between 2006 and 2012 according to whether postoperative chemotherapy was planned or not.

Table 2. Univariate Cox-regression analyses of potential prognostic factors for disease-free survival and time to recurrence in stage II patients resected for rectal cancer in Sweden between 2006 and 2012.

	Disease-free survival			Time to recurrence		
	HR	95% CI	p	HR	95% CI	p
Age (year)						
<60	1.00			1.00		
61–69	1.21	.94–1.55	.145	.86	.64–1.15	.313
70–79	1.73	1.35–2.18	<.001	.91	.68–1.12	.504
≥80	3.17	2.46–4.00	<.001	.80	.80–1.13	.204
Gender						
Female	1.00			1.00		
Male	1.06	.92–1.23	.405	.94	.76–1.17	.596
ASA score						
1–2	1.00			1.00		
3–4	2.28	1.98–2.64	<.001	1.16	.91–1.49	.227
Distance to anal verge (cm)						
>10	1.00			1.00		
6–10	1.30	1.08–1.57	.005	1.57	1.19–2.07	.002
≤5	1.29	1.10–1.53	.003	1.42	1.09–1.84	.009
Preoperative RT						
No	1.00			1.00		
Yes	.82	.72–.94	.005	.85	.69–1.04	.116
Preoperative CRT						
No	1.00			1.00		
Yes	.99	.82–1.19	.884	1.82	1.44–2.31	<.001
Intraoperative bowel perforation						
No	1.00			1.00		
Yes	1.84	1.43–2.37	.001	1.59	1.06–2.39	.025
Bowel resection						
Anterior resection	1.00			1.00		
Abdominoperineal excision	1.56	1.33–1.82	.001	1.53	1.21–1.92	<.001
Hartman's operation	2.78	2.33–3.32	.001	1.92	1.45–2.56	<.001
Tumor differentiation						
Moderately + well differentiated	1.00			1.00		
Poorly differentiated	1.23	.99–1.52	.057	1.50	1.11–2.03	.009
T stage						
pT3	1.00			1.00		
pT4	1.89	1.55–2.30	<.001	2.07	1.56–2.76	<.001
Mucinous cancer						
No	1.00			1.00		
Yes	1.26	1.03–1.53	.024	1.30	.97–1.75	.084
Examined number of lymph nodes						
0–11	1			1		
12–21	.82	.70–.96	.014	.82	.65–1.04	.102
>22	.65	.53–.80	<.001	.60	.44–.81	.001
Perineural invasion						
No	1.00			1.00		
Yes	1.49	1.21–1.84	<.001	2.22	1.69–2.93	<.001
Lymphovascular invasion						
No	1.00			1.00		
Yes	1.16	.96–1.40	.135	1.53	1.18–1.98	.001
Postoperative chemotherapy						
No	1.00			1.00		
Yes	.96	.78–1.19	.710	1.77	1.37–2.27	<.001

CI: confidence interval; CRT: chemoradiotherapy; RTL: radiotherapy.

More than 22 examined lymph nodes correlated to a better TTR (Table 4).

Discussion

In this population-based national study on 2649 rectal cancer patients with TNM stage II (T3–4N0M0) disease, those with LVI and/or PNI had a significantly higher risk of recurrence, whether local or distant. Patients with LVI and PNI were more often considered for postoperative chemotherapy than those without these factors (25% vs. 31% and 13%, respectively). The DFS was poorer in patients with either LVI or PNI. To our knowledge, the current study represents the largest evaluation of patients with LVI and PNI for stage II rectal

cancer operated with a total mesorectal excision after having received risk adapted preoperative RT or CRT, and may offer the best evidence regarding the risk of recurrence in this group.

In the present study, the rate of LVI was 15% which is comparable with that observed in other reports [13,22,23]. The reported rates of LVI in stage III CRC is, however, higher (20–30%) [24–26]. In stage IV CRC, Sternberg et al. detected venous invasion with hematoxylin and eosin (H&E) and elastic fiber stain in 70% of the specimens [27]. A higher detection rate of LVI in CRC with elastic stain is also reported by others [28,29]. In a meta-analysis by Yang et al. [30], PNI was significantly associated with poor DFS and increased risk of recurrence in CRC patients, and the detection rate in rectal cancer patients (stage I–III) was 19%. The detection rate of

10% in the present study for stage II on a national level is comparable with previously published data, where the object was not specific PNI detection. In a retrospective study of stage II rectal cancer, the PNI detection rate was 8% and rose to 24% after reevaluation of H&E stained specimens [31].

Table 3. Multivariate Cox-regression analysis of potential prognostic factors for disease-free survival in stage II patients resected for rectal cancer in Sweden between 2006 and 2012.

	Disease-free survival		
	HR	95% CI	p
Age (year)			
<60	1.00		
61–69	1.12	.86–1.45	.393
70–79	1.45	1.13–1.86	.004
>80	2.12	1.62–2.76	<.001
ASA score			
1–2	1.00		
3–4	1.69	1.44–1.97	<.001
Bowel resection			
Anterior resection	1.00		
Abdominoperineal excision	1.24	1.05–1.46	.013
Hartmann's operation	1.74	1.43–2.12	<.001
Intraoperative bowel perforation			
No	1.00		
Yes	1.44	1.11–1.87	.007
Examined number of lymph nodes			
0–11	1		
12–21	.91	.77–1.07	.230
>22	.71	.58–.88	.001
T stage			
pT3	1.00		
pT4	1.64	1.33–2.03	<.001
Perineural invasion			
No	1.00		
Yes	1.37	1.10–1.69	.005

CI: confidence interval.

Included variables: Age, ASA-score, distance to anal verge, preoperative radiotherapy, intraoperative bowel perforation, bowel resection, T stage, mucinous tumor, examined number of lymph nodes, perineural invasion.

The findings of this report as regards prognostic factors are based on a large patient cohort, which were not the case in any of the published randomized trials on adjuvant chemotherapy in rectal cancer [21,32–34]. In the PROCTOR/SCRIPT study, only 72 patients had stage II [21]. Additionally, almost all patients in the present study underwent preoperative staging with MRI, selecting patients for preoperative RT and CRT in contrast to, for example the EORTC 22921 study, in which patient selection was based on clinical and computer tomography findings [34].

There are some limitations in our study such as the inherent risk of registration bias and the lack of consistent validation. Previous validation on several variables in the SCRCR against medical records, has shown the validity to be good [20,35]. A major concern of the present study is the lack of differentiation between venous and lymphatic vessel invasion, but one should keep in mind that venous invasion is easier to detect than lymphatic invasion on H&E staining, and few pathological departments have routinely used other stainings or immunohistochemical staining for elastin to detect LVI during the study period. Furthermore, the risk of false positive cases with LVI must be regarded as small and based on erroneous registration. Nonetheless, there is a considerable risk of false negative cases as the study was retrospective and based on registered data. From previous studies, we also know that not all patients allocated to chemotherapy actually received this treatment. Information about whether adjuvant chemotherapy was initiated or not is available in the SCRCR since 2009, showing that the treatment was initiated in 70% of the patients considered for the adjuvant chemotherapy. In the I-CNR-RT study, 70% of patients randomized to chemotherapy actually commenced the treatment. In a previous study on the SCRCR, 70% of

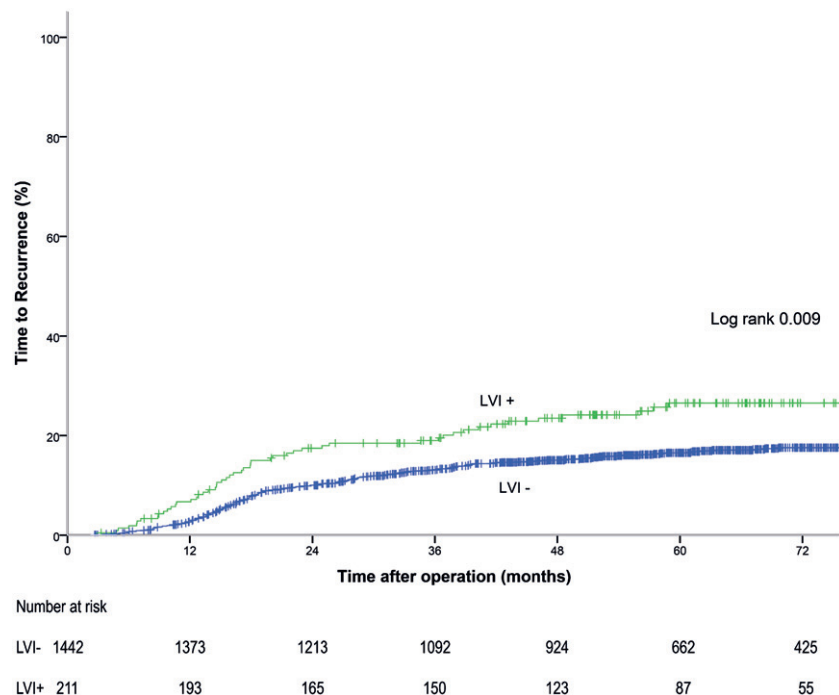


Figure 2. Time to recurrence in stage II rectal cancer patients in Sweden between 2006 and 2012 without postoperative chemotherapy, according to lymphovascular invasion.

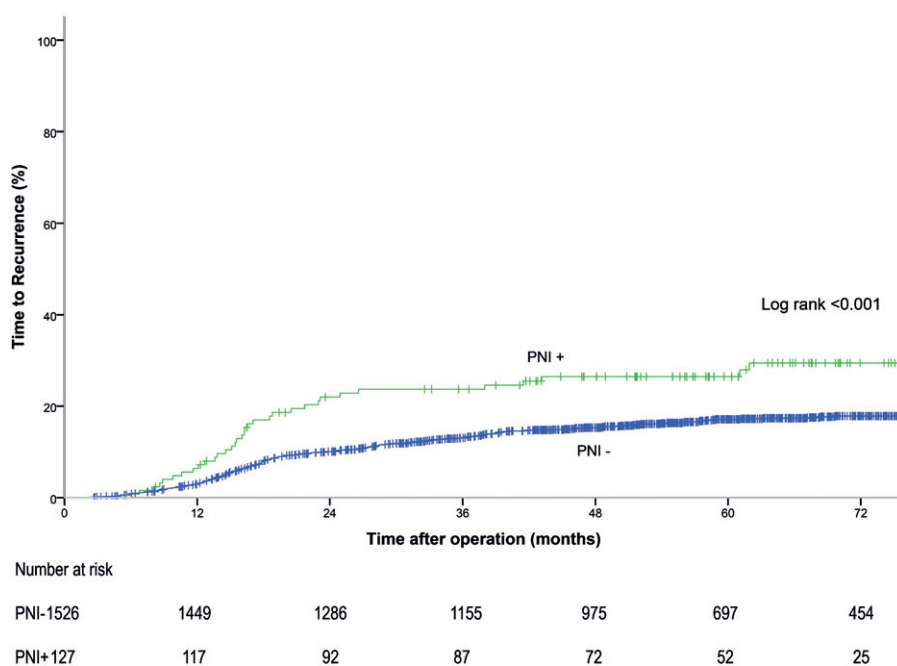


Figure 3. Time to recurrence in stage II rectal cancer patients in Sweden between 2006 and 2012 who were not planned for postoperative chemotherapy, according to perineural invasion.

Table 4. Multivariate Cox-regression analysis of time to recurrence in stage II rectal cancer patients.

	Time to recurrence		
	HR	95% CI	p
Preoperative CRT			
No	1.00		
Yes	1.65	1.29–2.12	<.001
Bowel resection			
Anterior resection	1.00		
Abdominoperineal excision	1.28	1.01–1.63	.043
Hartman’s operation	1.86	1.40–2.49	<.001
Examined number of lymph nodes			
0–11	1		
12–21	.92	.73–1.16	.571
>22	.65	.47–.89	.007
T stage			
pT3	1.00		
pT4	1.62	1.20–2.19	.002
Lymphovascular invasion			
No	1.00		
Yes	1.44	1.09–1.90	.011
Perineural invasion			
No	1.00		
Yes	1.80	1.34–2.43	<.001

CI: confidence interval; CRT: chemoradiotherapy. Included variables: tumor distance to anal verge, preoperative chemoradiotherapy, type of bowel resection, intraoperative bowel perforation, number of examined lymph nodes, T stage, tumor differentiation, perineural and lymphovascular invasion and adjuvant chemotherapy.

patients with stage III rectal cancer were planned for postoperative chemotherapy but only 75% of those actually started the treatment [36]. An awareness of these latter facts actually strengthens our findings of the prognostic importance of LVI and PNI.

Although the Swedish national guidelines between 2006 and 2012 did not recommend adjuvant chemotherapy to rectal cancer patients, one in seven patients with stage II rectal cancer were considered for this, and it was then initiated in the majority of them. However, this proportion was, besides patient-related factors such as age, absence of co-morbidity,

dependent upon risk factors such as advanced T stage, LVI and PNI, all known to be prognostic in colon cancer [37]. This reflects the difficulties clinical oncologists face in everyday clinical practice. There is no strong scientific evidence to routinely recommend adjuvant chemotherapy to stage II rectal cancer patients, particularly not after preoperative therapy; however, the risk of recurrence is 15–20% at three years, and this implies that specific prognostic pathological or other features to select patients who have the greatest potential benefit from adjuvant chemotherapy are required. A more precise pathological examination regarding differentiation of LVI and more specific description of PNI is warranted.

In conclusion, stage II rectal cancer patients with LVI and PNI have an increased risk of recurrence and a poorer DFS. These findings emphasize the need of future prospective evaluation on the role of adjuvant chemotherapy in stage II rectal cancer with specific pathological risk factors such as LVI and PNI.

Ethical standards

The study was approved by the local ethics committee of Uppsala University, Sweden and followed the Declaration of Helsinki guidelines.

Disclosure statement

The authors declare no conflict of interest.

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