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Defining a high-risk subgroup with colon cancer stages I and II for possible adjuvant therapy

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ABSTRACT

Aim: Adjuvant therapy is not routinely recommended in UICC stages I and II colon cancer, but may be considered for high-risk patients. Our aim is to identify clinicopathologic characteristics in colon cancer stages I and II, which are associated with an increased risk of tumour recurrence and tumour-related death.

Methods: We analysed our prospectively documented clinical database of 775 patients with colon cancer stages I and II, which underwent curative resection between 1982 and 2006. No adjuvant chemotherapy was applied. The median follow-up time was 80 months.

Results: For the entire study group, 5- and 10-year tumour-specific survival probabilities were 94.8 ± 0.9% and 91.0 ± 1.4%, respectively. Multivariate analysis identified three tumour characteristics as independent prognostic factors: lymphatic vessel invasion ($p = 0.034$), poor tumour grading (G3/G4) ($p = 0.020$) and extended tumour length ($\geqslant 6$ cm) ($p = 0.042$). Five-year (10-year) tumour-specific survival for patients without any of the poor prognostic tumour characteristics (ppTCs) was 96.0% (94.7%). There was a significantly increased risk for tumour-related death with increasing numbers of ppTCs ($p < 0.001$). While patients with only one ppTC had a 5-year (10-year) tumour-specific survival of 94.8% (88.9%), it decreased to 88.9% (78.4%) for patients with two ppTCs (hazard ratio (HR) 3.69, 95% confidence interval (CI) 1.67–8.13) and to 87.5% (72.9%) for patients with all three ppTCs (HR 6.56, 95% CI 1.50–26.62).

Conclusion: Patients with stage I or II colon cancer have a favourable prognosis after radical resection. The presence of two or three poor prognostic tumour characteristics identifies a small patient subgroup (12%) with an increased risk of tumour-related death that may be considered for adjuvant chemotherapy.

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1. Introduction

The mainstay therapy for colon cancer without distant metastases is oncologic resection.[1] Current recommendations for adjuvant treatment are based on the risk stratification according to the UICC staging classification.[2,3] Adjuvant chemotherapy is recommended in stage III colon cancer as it has proved to reduce the rate of tumour recurrence, to increase disease-free and overall survival and to be cost-effective in this patient group.[4] For colon cancer stages I and II, however, the available randomised controlled trials (RCTs), reviews, pooled analyses and meta-analyses have failed to demonstrate convincing survival benefits for the entire patient group.[5–9] Based on these data, the American Society

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of Clinical Oncology issued a guideline stating 'direct evidence from randomised controlled trials does not support the routine use of adjuvant chemotherapy for patients with stage II colon cancer'.[5] At the same time, however, adjuvant chemotherapy is administered to a significant proportion (27%) of patients with stage II colon cancer despite the uncertainty regarding the significance or magnitude of benefit.[10] And the German S3-Guideline 'Colorectal Cancer' 2004/2008 states 'in patients with curatively resected colon carcinoma stage II, adjuvant chemotherapy *can be administered*' and 'in stage II, adjuvant chemotherapy *should be considered in selected risk situations*'.[11]

While there is no doubt that the majority of stages I and II colon cancer patients are indeed cured by surgery alone and might be overtreated and unnecessarily subjected to the side-effects of adjuvant therapy, some patients, nevertheless, relapse and subgroups with high-risk characteristics for tumour recurrence might benefit from adjuvant therapy. Therefore, the patient selection criteria for adjuvant therapy in colon cancer stages I and II have to be clearly defined. The aim of this study is to identify clinicopathologic characteristics in colon cancer stages I and II which are associated with an increased risk for tumour recurrence and tumour-related death, thus defining a high-risk subgroup that might be considered for and potentially benefit from adjuvant therapy.

2. Patients and methods

2.1. Study cohort

In our colorectal database, we prospectively documented all patients who underwent surgical resection for colorectal cancer in our department. Starting in 1982, this database includes a total of 3026 colorectal cancer patients with data on patient characteristics, preoperative tumour staging, preoperative multimodal treatment, details of the surgical procedure, occurrence of complications, postoperative histopathology, application of adjuvant or palliative treatment and follow-up. In this prospectively conducted colorectal database, we searched for patients who underwent curative resection (R0) for colon cancer stages I and II (pT1–4, N0, M0) between 1982 and 2006. As an indirect measure for the quality of surgery over this 25-year period, the median number of resected lymph nodes ranged between 13 and 20 in all the five time periods analysed (Table 1). Patients with rectal cancer (i.e. adenocarcinoma 0–16 cm from the anal verge by rigid rectoscopy) and patients with carcinoma in situ of the colon were not included. Patients with colon cancer stages I and II who received adjuvant therapy ($n = 31$) were excluded. Altogether, 782 consecutive patients with stages I and II colon cancer without adjuvant therapy were identified. As follow-up data were not available for seven patients, the final study group for this analysis consisted of 775 patients.

2.2. Treatment

Preoperatively, all patients, unless obstructed, underwent complete colonoscopy for histological confirmation of colon cancer and to rule out synchronous disease. Staging examinations included chest X-ray, abdominal ultrasound and/or computed tomography (CT). All patients underwent standardised curative oncologic resection in our department. Tumours located in the caecum, ascending colon, right (hepatic) flexure and right-sided transverse colon ($n = 361$) were resected by (extended) right-sided hemicolectomy. Patients with tumours in the left-sided transverse colon, left (splenic) flexure, descending colon and sigmoid colon ($n = 414$) underwent (extended) left-sided hemicolectomy or radical sigmoid resection. Standardised oncologic lymphadenectomy was performed in all cases.

Table 1 – Patient characteristics and histopathologic parameters of 775 consecutive patients with colon cancer stages I and II.

Parameter	Category	No. of patients (%)[a]
Age	Median (interquartile range)	67.0 (59–75)
Gender	Male	423 (55%)
	Female	352 (45%)
Year of operation	1982–1985	60 (8%)
	1986–1990	98 (13%)
	1991–1995	148 (19%)
	1996–2000	218 (28%)
	2001–2006	251 (32%)
Tumour location	Right colon	361 (47%)
	Left colon	414 (53%)
Tumour length	<2 cm	90 (12%)
	⩾2 and <6 cm	461 (59%)
	⩾6 cm	224 (29%)
Obstruction	Absent	713 (92%)
	Present	62 (8%)
Perforation	Absent	769 (99%)
	Present	6 (1%)
Grading	G1 or G2	606 (78%)
	G3 or G4	169 (22%)
pT	1	118 (15%)
	2	165 (21%)
	3	418 (54%)
	4	74 (10%)
Lymphatic vessel invasion	Absent	712 (92%)
	Present	63 (8%)
Angioinvasion	Absent	765 (99%)
	Present	10 (1%)
No. of lymph nodes analysed	Median (interquartile range)	17.0 (12–23)
	<12	129 (17%)
	⩾12	646 (83%)

a Unless otherwise indicated under category.

2.3. Histopathologic analysis

All resection specimens were examined according to a standardised histopathologic protocol with evaluation of the UICC TNM-category.[2] Complete tumour resection (R0 resection) was achieved in all cases. Multiple additional clinicopathologic features like tumour obstruction (defined as either clinically evident obstructive ileus ($n = 27$) or complete

Table 2 – Multivariate Cox Regression analysis for clinicopathologic features of 775 consecutive patients with colon cancer stages I and II for tumour-specific survival.

Parameter	Hazard ratio	95% Confidence interval	*p*-Value
Sex			0.465
Male versus female[a]	0.796	0.431–1.469	
Age			0.138
Continuous	1.020	0.994–1.048	
Year of operation			**<0.001**
Continuous	0.874	0.828–0.923	
Tumour location			0.643
Right versus left hemicolon[a]	1.157	0.624–2.147	
Lymph nodes analysed			0.637
Continuous	0.993	0.967–1.021	
Lymphatic vessel invasion			**0.034**
Absent versus present[a]	2.369	1.068–5.255	
Tumour grading			**0.020**
G1/G2 versus G3/G4[a]	2.185	1.129–4.226	
Tumour length			**0.042**
<2 cm[a]	1.0	–	
⩾2 cm and <6 cm	4.265	0.569–31.961	
⩾6 cm	7.855	1.016–60.705	

a Reference category.

endoscopic tumour obstruction ($n = 35$)), tumour perforation, tumour length (defined as the maximum diameter of the tumour in the opened colon resection specimen), angioinvasion and lymphatic vessel invasion were also prospectively documented.

2.4. Follow-up

All 775 patients were followed regularly according to the guidelines of the German Cancer Society. The last follow-up was completed for all patients on 15th September 2008. The median follow-up time was 80 months (interquartile range (iqr) 45–115 months). In suspicion of local or distant tumour recurrence, every effort was undertaken for histological confirmation.

2.5. Statistical analysis

Statistical analysis was performed by using the SPSS software package (version 15.0, SPSS, Chicago, IL). Descriptive statistics were reported for relevant variables. Univariable analysis of tumour-specific survival was performed for all parameters listed in Table 1 using the Kaplan–Meier method to estimate survival probabilities in patient subgroups and the log-rank test for statistical comparisons. Since the Kaplan–Meier approach was used to estimate 5- and 10-year survival probabilities, patients with shorter follow-up times were also considered within this calculation up to the end of their observation. To investigate multivariable relationships of covariates with survival, Cox proportional hazard models with variable selection procedures were performed (Table 2). All statistical comparisons were considered statistically significant at a two-sided p-value < 0.05. Since this study was conducted in an explorative manner, no adjustment of overall alpha error level was performed to avoid over-conservatism. Concerning this matter, we followed a more practical solution: as suggested by Saville,[12] corrections for multiple comparisons are not performed but all available data and comparisons made are honestly reported allowing the reader to draw the conclusions. So the reader can informally adjust for multiple comparisons while reviewing the data.

3. Results

3.1. Patient characteristics and histopathologic parameters

Table 1 shows the patient characteristics and the histopathologic parameters of our study group of 775 patients.

3.2. Survival

For the entire study group, 5- and 10-year tumour-specific survival probabilities were 94.8 ± 0.9% and 91.0 ± 1.4%, respectively. The 283 patients (36%) with colon cancer stage I had 5- and 10-year tumour-specific survival probabilities of 98.7 ± 0.7% and 95.6 ± 1.7%, respectively (Fig. 1). For the 492 patients (64%) with colon cancer stage II, the 5- and 10-year tumour-specific survival rates were 92.5 ± 1.4% and 88.4 ± 1.9%, respectively (Fig. 1). Statistically, stage I patients had a significantly better tumour-specific survival than stage II patients ($p = 0.003$). During follow-up, 67 patients (8.6%) developed recurrent disease, with distant metastases in 50 cases (6.4%) and local recurrences in 17 cases (2.2%), and 46 patients (5.9%) died of tumour recurrence. Tumour-related deaths occurred in 7/283 patients with stage I colon cancer (2.5%) and in 39/492 patients with stage II colon cancer (7.9%).

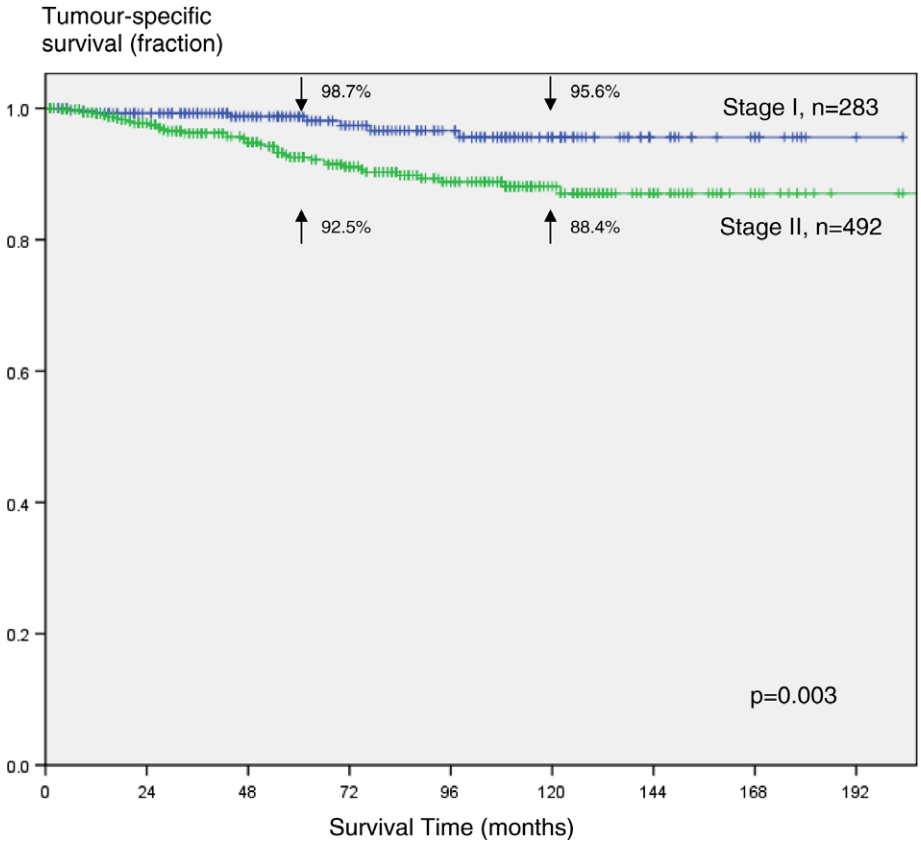

Fig. 1 – Kaplan–Meier survival curve for tumour-specific survival of 283 patients with stage I colon cancer and 492 patients with stage II colon cancer.

3.3. *Identification of risk factors*

Patient characteristics and histopathologic parameters were analysed for their prognostic relevance. In multivariable Cox Regression analysis, four parameters proved to be independent prognostic factors for tumour-specific survival: early years of operation ($p < 0.001$), presence of lymphatic vessel invasion ($p = 0.034$), poor tumour grading ($p = 0.020$) and extended tumour length ($p = 0.042$) (Table 2). For risk stratification to identify a high-risk patient subgroup, all patients were grouped according to the presence of these poor prognostic tumour characteristics (ppTCs), i.e. presence of lymphatic vessel invasion, G3/G4 'high grade' tumour and/or tumour length $\geqslant 6$ cm. Fig. 2 and Table 3 illustrate that 5- and 10-year tumour-specific survival were significantly decreased from patients without any ppTC (96.0 ± 1.1% and 94.7 ± 1.3%, respectively) over patients with one ppTC (94.8 ± 1.6% and 88.9 ± 2.9%, respectively) to patients with two ppTCs (88.9 ± 4.0% and 78.4 ± 7.0%, respectively) and patients with three ppTCs (87.5 ± 11.7% and 72.9 ± 16.5%, respectively) ($p < 0.001$). The relative risk of tumour recurrence and the relative risk of tumour-specific death significantly increased with the number of ppTCs (Table 3). Using this risk stratification, the group of patients with two or three ppTCs is clearly identified as the 'high-risk' subgroup for tumour recurrence and tumour-related death (Table 3).

3.4. *Stage-specific analysis*

Table 4 shows the stage-specific subgroup analysis separately for stage I patients and for stage II patients. In stage I disease, 207 patients with no ppTC had a better recurrence-free and tumour-specific survival than 67 patients with one ppTC. However, only eight patients with stage I colon cancer showed two ppTCs and none showed all three ppTCs. In stage II, the results of the risk stratification using the ppTCs are similar to the results of the entire stages I and II groups with increasing risks for both tumour recurrence and tumour-related death with increasing number of ppTCs.

4. Discussion

Patients with UICC stages I and II colon cancer have a favourable prognosis after oncologic resection with reported 5-year survival rates of about 90% and 80%, respectively.[13,14] In our study group, treated with oncologic surgery alone, tumour-specific survival was excellent with about 95% 5-year tumour-specific survival and 91% 10-year tumour-specific survival. Given these survival estimates, the routine use of adjuvant therapy for all stages I and II colon cancer patients appears unjustified: the majority of patients are indeed cured by surgery alone and would be overtreated and unnecessarily subjected to the side-effects of adjuvant therapy.[4]

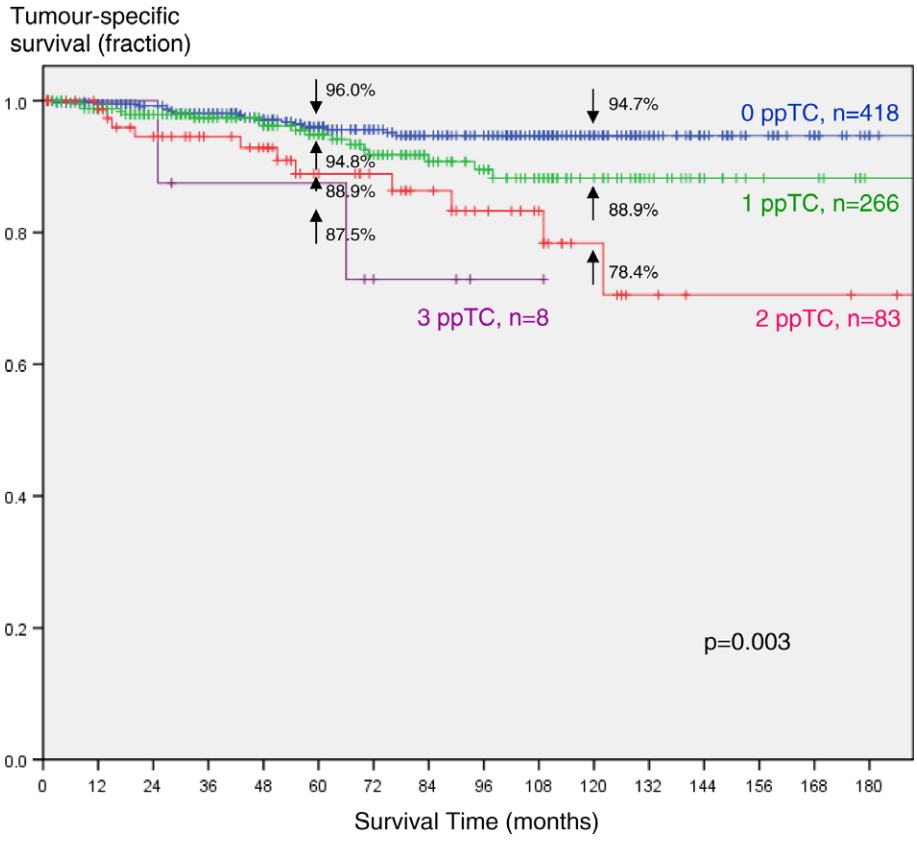

Fig. 2 – Kaplan–Meier survival curve for 418 patients without any poor prognostic tumour characteristics (ppTCs), for 266 patients with 1 ppTC, 83 patients with 2 ppTCs and 8 patients with all 3 ppTCs; poor prognostic tumour characteristics are: presence of lymphatic vessel infiltration, poor tumour differentiation (G3/G4) and tumour length ⩾ 6 cm.

Table 3 – Risk stratification for recurrence-free survival and tumour-specific survival of 775 consecutive patients with colon cancer stages I and II using the presence of the identified poor prognostic tumour characteristics (ppTCs).

Patient group	Five-year RFS (mean ± SD)	Ten-year RFS (mean ± SD)	Hazard ration	95% CI	*p*-Value
(a) Recurrence-free survival (RFS)					
All patients (n = 775)	90.9 ± 1.2%	88.1 ± 1.4%			
0 ppTC (n = 418)	93.5 ± 1.3%	92.5 ± 1.5%	1		p = 0.004
1 ppTC (n = 266)	89.0 ± 2.3%	85.2 ± 2.9%	1.83	1.06–3.17	0.031
2 ppTCs (n = 83)	83.8 ± 4.5%	76.8 ± 6.4%	3.03	1.55–5.92	0.001
3 ppTCs (n = 8)	75.0 ± 15.3%	75.0 ± 15.3%	4.50	1.07–19.01	0.04
	Five-year TSS (mean ± SD)	Ten-year TSS (mean ± SD)			
(b) Tumour-specific survival (TSS)					
All patients (n = 775)	94.8 ± 0.9%	91.0 ± 1.4%			
0 ppTC (n = 418)	96.0 ± 1.1%	94.7 ± 1.3%	1		p = 0.003
1 ppTC (n = 266)	94.8 ± 1.6%	88.9 ± 2.9%	1.81	0.90–3.62	0.094
2 ppTCs (n = 83)	88.9 ± 4.0%	78.4 ± 7.0%	3.69	1.67–8.13	0.001
3 ppTCs (n = 8)	87.5 ± 11.7%	72.9 ± 16.5%	6.56	1.50–26.62	0.012

While many trials have confirmed Moertel's first report on survival benefits for adjuvant therapy in patients with stage III colon cancer,[8,15–18] its value has remained doubtful in stage II disease because most studies have failed to show a significant survival benefit.[5–7,9] Only few reports show a significant benefit of adjuvant therapy for stage I and/or II colon cancer. Wolmark et al. showed a 12% improvement in survival (p = 0.005) in a subgroup analysis of Dukes' B patients with portal vein infusion of fluorouracil compared with surgery alone.[19,20] A meta-analysis of individual patient data including 10 trials, comparing fluorouracil-based chemotherapy by portal vein infusion to surgery alone, showed a reduction in the annual odds of death for the subgroup of Dukes' A and B patients of 27% and 18%, respectively, translating into a 5% absolute

Table 4 – Risk stratification by UICC stage groups for recurrence-free survival and tumour-specific survival using the identified poor prognostic tumour characteristics (ppTCs) for 283 patients with colon cancer stage I and for 492 patients with colon cancer stage II.

Patient group	Five-year RFS (mean ± SD)	Ten-year RFS (mean ± SD)	*p*-Value
(a) Stage I (n = 283): recurrence-free survival (RFS)			
Stage I (*n* = 283)	95.5 ± 1.4%	94.7 ± 1.6%	
0 ppTC (*n* = 207)	96.5 ± 1.4%	95.5 ± 1.7%	n.s.
1 ppTC (*n* = 67)	91.3 ± 4.4%	91.3 ± 4.4%	
2 ppTCs (*n* = 9)	100%	100%	
3 ppTCs (n = 0)	–	–	
	Five-year TSS (mean ± SD)	Ten-year TSS (mean ± SD)	
(b) Stage I (n = 283): tumour-specific survival (TSS)			
Stage I (*n* = 283)	98.7 ± 0.7%	95.6 ± 1.7%	
0 ppTC (*n* = 207)	98.8 ± 0.8%	97.0 ± 1.5%	n.s.
1 ppTC (*n* = 67)	98.4 ± 1.6%	88.3 ± 7.2%	
2 ppTCs (*n* = 9)	100%	100%	
3 ppTCs (*n* = 0)	–	–	
	Five-year RFS (mean ± SD)	Ten-year RFS (mean ± SD)	
(c) Stage II (n = 492): recurrence-free survival (RFS)			
Stage II (*n* = 492)	88.2 ± 1.6%	84.4 ± 2.0%	
0 ppTC (*n* = 211)	90.6 ± 2.2%	89.6 ± 2.4%	$p = 0.002$
1 ppTC (*n* = 199)	88.3 ± 2.6%	83.5 ± 3.5%	
2 ppTCs (*n* = 74)	82.0 ± 5.0%	74.7 ± 6.7%	
3 ppTCs (*n* = 8)	75.0 ± 15.3%	75.0 ± 15.3%	
	Five-year TSS (mean ± SD)	Ten-year TSS (mean ± SD)	
(d) Stage II (n = 492): tumour-specific survival (TSS)			
Stage II (*n* = 492)	92.5 ± 1.4%	88.4 ± 1.9%	
0 ppTC (*n* = 211)	93.2 ± 2.0%	92.3 ± 2.2%	$p < 0.001$
1 ppTC (*n* = 199)	93.9 ± 2.0%	89.1 ± 3.1%	
2 ppTCs (*n* = 74)	87.5 ± 4.5%	81.4 ± 5.9%	
3 ppTCs (*n* = 8)	87.5 ± 11.7%	72.9 ± 16.5%	

5-year survival benefit in the subgroup of Dukes' A and B patients ($p = 0.01$).[21] More recently, Gill et al. compared surgery alone to surgery plus adjuvant chemotherapy (FU + leucovorin or FU + levamisole) in a pooled analysis of seven RCTs including 3302 patients with stages II and III colon cancer.[8] For the subgroup of 1440 stage II patients, the improvement with adjuvant chemotherapy did reach statistical significance for 5-year disease-free survival (76% versus 72%; $p = 0.0490$) but did not for 5-year overall survival (81% versus 80%; $p = 0.1127$).[8] Most recently, the QUASAR trial on 3,239 patients with completely resected stage I, II or III colon or rectal cancer and 'uncertain indication for chemotherapy' showed a reduced relative risk of tumour recurrence ($p = 0.01$) and of dying from colorectal cancer ($p = 0.008$) with chemotherapy as compared to observation for the entire patient group.[22] For the subgroup of stage II colon cancer, however, the relative risk of dying from colon cancer is not shown in the QUASAR trial and the observed reduced relative risk of recurrence (RR 0.71; 95% confidence interval (CI) 0.54–0.92; $p = 0.01$) is only valid for the 2 years after randomisation but not over the whole study period.[22] Overall, all these 'positive' results on adjuvant therapy for colon cancer stage I and/or II are derived from subgroup analyses inappropriate for formulation of treatment standards. Besides, some of these trials improperly accepted <12 lymph nodes to diagnose stage II disease.[23,24]

Nevertheless, controversy on the administration of adjuvant therapy for stages I and II colon cancer patients still persists for several reasons. First, adjuvant chemotherapy has already proven beneficial for other malignancies with comparably favourable prognosis, such as breast cancer. Second, given the compelling benefit and low adverse effects of adjuvant therapy in stage III disease, it appears biologically implausible that adjuvant treatment for stages I and II disease would not confer at least some degree of benefit. Third, almost all the data on adjuvant therapy in stages I and II disease are derived from RCTs that included a large proportion of stage III patients and, very likely, too few stages I and II patients to definitely determine the benefit of adjuvant therapy in these stage groups. It has been calculated that a RCT on adjuvant chemotherapy in colon cancer stage II with a surgery alone control arm and an estimated baseline prognosis of 80% would require a sample size of about 5000 patients.[5,25] Furthermore, 5-year survival may be an insufficient measure of long-term outcome for colon cancer patients with node-negative disease.

A means to increase the effect of adjuvant treatment is to identify those patients that are expected to benefit most from adjuvant therapy, i.e. most likely, the patients with the highest risk for tumour recurrence. In our study group, about 6% of the patients died of tumour recurrence. These

are the patients that have to be identified. However, the traditional UICC staging system fails to do so. And indeed, most discussions on adjuvant therapy in stages I and II colon cancer finally come down to the identification of risk factors in addition to UICC stage groups.[11,26] Therefore, we searched for clinicopathologic features to define this high-risk subgroup most accurately. In our explorative investigation, no adjustment of overall alpha error level was conducted because of the natural difficulty in this type of investigation and to avoid over-conservatism, However, aware of the so called 'multiple test problem', we followed a more practical solution: as suggested by Saville, corrections for multiple comparisons are not performed but all available data and comparisons made are honestly reported allowing the reader to draw the conclusions.[12] In our cohort, we identified three ppTCs defining subgroups with increased risk for tumour-specific death. Patients with only one ppTC had a slightly decreased tumour-specific survival compared with patients with no ppTC. The high-risk subgroups in our analysis are the groups of patients with two or three ppTCs. This risk stratification renders similar results for the entire patient cohort and for stage II patients only. For stage I disease, the risk stratification also discriminates patients with no ppTC from patients with one ppTC, but reveals only eight patients with two ppTCs and none with three ppTCs, inadequate for proper statistical analysis.

In the literature, it has been repeatedly reported on 'high-risk' patients with stage I or II colon cancer, however, all too often without clearly defining this term. Several studies identified the following as poor prognostic factors: inadequate number of sampled lymph nodes,[27,28] T4 lesions, tumour perforation, lymphatic vessel invasion or poorly differentiated histology.[8,18,29–31] The latter two were also identified in our study and were stratified as category IIA and category I prognostic factor in colorectal carcinoma by the College of American Pathologists Consensus Statement 1999, respectively.[30] Tumour length came up as the third ppTC in our study group most likely due to its strong correlation with pT-category and UICC stage in our cohort of exclusively node-negative patients, assuming that tumour size and grade matter in node-negative colon cancer just like they matter in other malignancies. While other studies investigated mainly molecular markers as additional poor prognostic factors for colon cancer,[5,29–37] we focused on the evaluation of commonly reported clinicopathologic features. These can easily be validated in other cohorts in addition to the UICC stages and might be helpful for the design of future trials on adjuvant therapy to achieve manageable sample sizes and reasonable follow-up periods.

In our study group, 12% of the patients had two or three of the identified ppTCs and showed significantly decreased 10-year disease-specific survival probabilities of 78% and 73%, respectively. With these numbers, patients are clearly uncomfortable as they might belong to the subgroup that relapses and dies. Hence, the decision to offer adjuvant therapy for stages I and II disease should be discussed in the light of the above mentioned evidence, must be individualised to the circumstances of each specific patient, and should be balanced against the possible risks of treatment-related toxicity. The survival data and risk factors identified in this analysis may assist oncologists in presenting objective prognostic information to patients and facilitate more informed decision-making on adjuvant chemotherapy in colon cancer stages I and II.

5. Conclusion

Patients with UICC stage I or II colon cancer have a very good prognosis after radical resection. The presence of multiple ppTCs, however, identifies a small high-risk subgroup. The risk stratification presented in this work may help to discriminate the patients cured by surgery alone from those patients that may benefit from adjuvant therapy, i.e. those at highest risk for recurrence.

Conflict of interest statement

None declared.

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