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Completeness of pathology reports in stage II colorectal cancer

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ABSTRACT

Introduction: The completeness of the pathological examination of resected colon cancer specimens is important for further clinical management. We reviewed the pathological reports of 356 patients regarding the five factors (pT-stage, tumor differentiation grade, lymphovascular invasion, tumor perforation and lymph node metastasis status) that are used to identify high-risk stage II colon cancers, as well as their impact on overall survival (OS).

Methods: All patients with stage II colon cancer who were included in the first five years of the MATCH study (1 July 2007 to 1 July 2012) were selected ($n = 356$). The hazard ratios of relevant risk factors were calculated using Cox Proportional Hazards analyses.

Results: In as many as 69.1% of the pathology reports, the desired information on one or more risk factors was considered incomplete. In multivariable analysis, age (HR: 1.07, 95%CI 1.04–1.10, $p < .001$), moderately- (HR: 0.35, 95%CI 0.18–0.70, $p = .003$) and well (HR 0.11, 95%CI 0.01–0.89, $p = .038$) differentiated tumors were significantly associated with OS.

Conclusions: Pathology reports should better describe the five high-risk factors, in order to enable proper patient selection for further treatment. Chemotherapy may be offered to stage II patients only in select instances, yet a definitive indication is still unavailable.

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Colorectal cancer; pathology reporting; prognostic factors

Introduction

Colorectal cancer is currently the second most common malignancy in the Western world [1]. Overall, 50–60% of the patients diagnosed with colorectal cancer will develop metastases [2–6]. The risk of developing metastases as well as survival can be estimated more accurately for the individual patient by taking into consideration the American Joint Committee on Cancer (AJCC) TNM classification [7]. The pathological TNM classification is the most important factor to determine the therapeutic approach [8].

For colon cancer, curatively resectable tumors are divided into AJCC stage I to III, with stage III necessitating adjuvant chemotherapy in addition to watchful waiting strategies. Patients with stage II colon carcinoma are thought not to require adjuvant chemotherapy in most cases [9,10]. However, the American Society of Clinical Oncology (ASCO) guidelines propose a subdivision of stage II patients into low and high-risk. This subdivision is based on five high-risk factors: T-stage, tumor differentiation grade, lymphovascular invasion (LVI), tumor perforation and, most importantly, lymph node metastasis status [9]. In high-risk patients, adjuvant chemotherapy can be considered, while adjuvant chemotherapy has no place in the treatment of low-risk stage II colon cancer patients [9,11].

Because of their importance and clinical implications, the pathology reports of colon cancer specimens should include a statement regarding the

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Supplemental data for this article can be accessed here.

five aforementioned factors. In addition to the five high-risk factors, molecular subtypes of cancer have been previously reported to have an effect on overall survival (OS) as well [12]. In particular, patients with microsatellite instability (MSI) are reported to have higher OS [12]. To optimize the accuracy of pathology reports on colorectal cancer specimens, the Dutch federation for pathology in 2008 drew up the guideline 'Protocol Colonrectum', summarizing which factors should be included in a pathology report and how [13]. The reporting of the five high-risk factors was facultative until early 2012, when the reporting of the factor LVI became mandatory [13].

In this study, a cohort of 356 patients was reviewed to determine the accuracy and completeness regarding the five factors used to identify high-risk stage II colon cancers. We performed a detailed analysis of nodal status, which is considered the most important risk factor [6].

Methods

Patient selection

Patients were selected from the MATCH study (MEC-2007-088), an ongoing prospective registration cohort including all patients who undergo curative surgery for primary colorectal cancer in seven hospitals in the Rotterdam region. All patients with stage II colon cancer who were included in the first five years of the MATCH study (1 July 2007 to 1 July 2012) were selected. All patients gave written informed consent.

Scoring pathology report

Pathology reports were examined for the existence of a statement on the five factors used to identify high-risk stage II patients: pathological T-stage (pT-stage), N-stage, tumor differentiation grade, LVI and tumor perforation. For the T-stage, tumor differentiation grade and LVI the presence or absence of a statement regarding these tumor characteristics was scored. For the N-stage, patients with more than 10 harvested lymph nodes were considered to have an N0 stage, while patients with less than 10 harvested lymph nodes were considered to have an Nx stage. In Nx patients, the presence or absence of a specific comment regarding the low total lymph node yield was scored. Tumor perforation was planned only to be scored present or absent in case of a clinical suspicion for perforation. As no patients had a clinical suspicion of tumor perforation, this factor was not scored. Data on MSI were not routinely scored. However, since MSI is highly correlated with right-sidedness of the tumor, we used this as a dummy variable [12]. Pathological risk factors associated with lower survival in stage II patients were individually examined in our patient cohort for both differences in clinicopathologic characteristics of patients, as well as survival analyses.

Statistical analysis

Summary statistics were provided as percentages of categorical variables and medians with interquartile ranges of continuous variables. Comparison of categorical variables was performed using the Pearson chi-square test, while continuous variables were compared using the Kruskal–Wallis test. OS estimates and figures were created using the Kaplan–Meier method. Patients who expired within three months postoperatively were excluded from the survival analysis. Differences in survival amongst the different risk factors were assessed using the Log-Rank test. The hazard ratios of relevant risk factors, along with their 95%CIs, were calculated using Cox Proportional Hazards analyses. Conditional backwards selection with all relevant risk factors was conducted, based on the probability of the likelihood-ratio statistic based on conditional parameter estimates. All analyses were carried out with SPSS 22 (IBM, Armonk, NY). All tests were two-sided and $p < .05$ was considered statistically significant.

Results

Pathology reports

As shown in Figure 1, in 69.1% of the pathology reports the information on one or more risk factors was considered incomplete (61.2% 1 factor, 7.9% 2 factors). T-stage and N-stage were reported in all cases. However, in the 44 Nx patients, the pathology report did not comment on this total yield as being a risk factor. In 62.8% of all cases, no statement regarding presence or absence of LVI was recorded; tumor differentiation grade was not reported in 2.3%. As mentioned in the introduction, the reporting of LVI became mandatory in 2012. LVI, regardless whether present or absent, was reported significantly more after mandating the reporting of this risk factor (33.5% vs. 87.5%; $p < .001$).

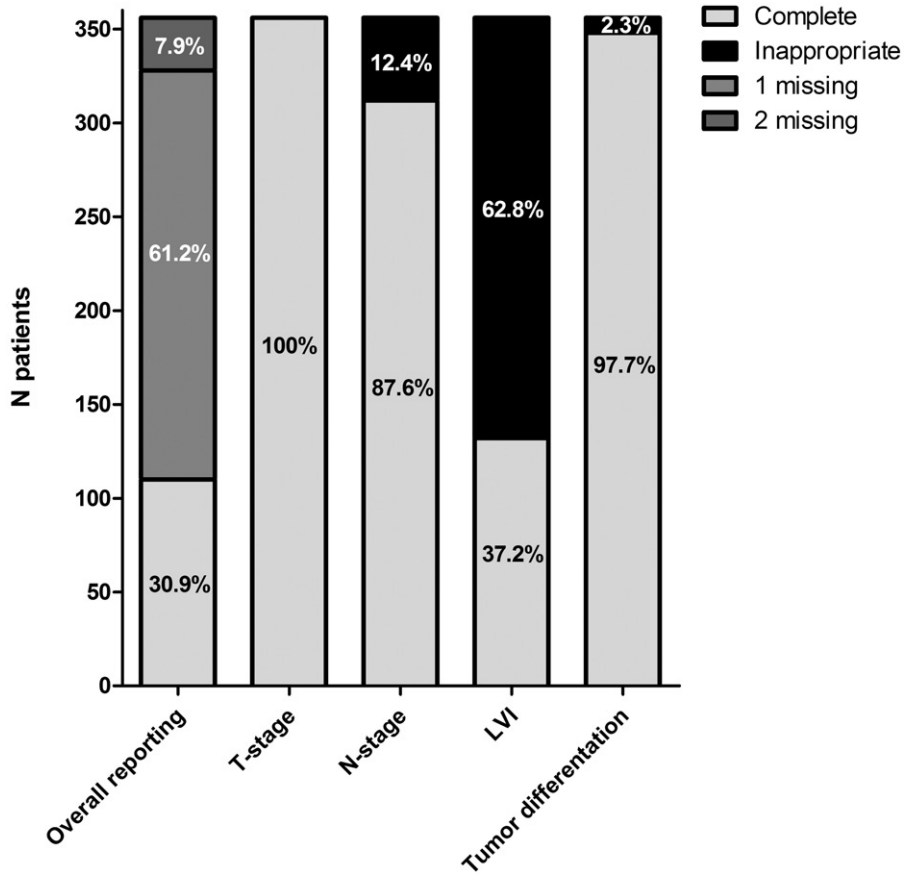

Figure 1. Overall reporting of high-risk factors (N-stage, T-stage, lymphovascular invasion, and tumor differentiation) in the pathology report. N-stage pathology report scoring. T-stage pathology report scoring. Lymphovascular invasion pathology report scoring. Tumor differentiation pathology report scoring.

Clinicopathological characteristics

Total baseline and other characteristics compared by N-stage are shown in Table 1. Just over half ($n = 193$, 54.2%) of the patients were male. The median age was 71 years (IQR 64–79 years). A diagnostic colonoscopy was performed in 327 (96.2%) of the patients and 320 (89.9%) patients underwent staging CT imaging. A small subgroup of patients received additional abdominal ultrasound ($n = 104$, 29.2%), MRI ($n = 8$, 2.2%), or PET-scan ($n = 1$, 0.3%). More than two-thirds of patients had an American Society of Anesthesiologists (ASA) classification score of 2 ($n = 195$, 70.1%). At the time of surgery, half of the patients underwent laparoscopic surgery ($n = 174$, 49.4%) and most patients underwent a right ($n = 172$, 49.0%) or left sided hemicolectomy ($n = 169$, 48.1%). The majority of patients had a T3 ($n = 324$, 91.0%), whereas a small minority had a T4 tumor ($n = 32$, 9.0%). Of our 356 patients, 312 (87.6%) patients did not have lymph node metastases and had more than 10 nodes, while 44 (12.4%) did not have the required minimum of 10 nodes. Over three quarters of the patients had a moderately differentiated tumor ($n = 298$, 83.9%). A small subgroup of patients ($n = 21$, 5.9%) received adjuvant therapy. In all, 13 patients (4.1%) expired within 90 days and were therefore excluded in survival analyses.

Differences between the patients with and without high-risk factors were more closely evaluated (Table 1, Supplementary Table 1–3). Between the Nx and N0 group, a significant difference was observed in median age, with the Nx group being significantly older (71 vs 75 years, $p = .029$). T4 patients as opposed to T3 patients received adjuvant chemotherapy (37.5% vs. 2.8%, $p < .001$) more often, and had an unknown (not reported) differentiation grade of their tumor relatively more frequently (9.4% vs. 1.5%, $p = .021$). No clinical differences were observed between patients with demonstrated LVI, patients without LVI, and patients in whom this factor was not recorded in the pathology report. Finally, there was a trend towards administering chemotherapy in patients with worse tumor differentiation ($p = .086$).

Overall survival per high-risk factor

Median follow-up in our cohort was 72.4 months (IQR 62.8–80.8). The 1-, 3- and 5-year survival was 98.0%, 89.1 and 80.4%, respectively. When

Table 1. Clinicopathological characteristics, stratified by nodal status.

Characteristic	N0 ($n = 312$)	Nx ($n = 44$)	p value	Total ($n = 356$)
Gender				
Female	139 (44.6)	24 (54.5)		163 (45.8)
Male	173 (55.4)	20 (45.5)	.213	193 (54.2)
Age, years (IQR)	71 (63–78)	75 (66–82)	.029	71 (64-79)
Diabetes	51 (16.9)	2 (4.7)	.037	53 (15.4)
Colonoscopy	285 (96.3)	42 (95.5)	.789	327 (96.2)
Abdominal ultrasound	94 (30.1)	10 (22.7)	.312	104 (29.2)
CT-abdomen	279 (89.4)	41 (93.2)	.439	320 (89.9)
MRI abdomen	7 (2.2)	1 (2.3)	.990	8 (2.2)
PET-scan	1 (0.3)	0 (0.0)	.707	1 (0.3)
ASA class				
1	31 (12.9)	1 (2.7)		32 (11.5)
2	167 (69.3)	28 (75.7)		195 (70.1)
3	43 (17.8)	8 (21.6)		51 (18.3)
4	0 (0.0)	0 (0.0)	.191	0 (0.0)
Type of operation				
Open resection	153 (49.5)	25 (58.1)		178 (50.6)
Laparoscopic resection	156 (50.5)	18 (41.9)	.289	174 (49.4)
Type of resection				
Left-sided resection	144 (46.8)	25 (58.1)		169 (48.1)
Right-sided resection	154 (50.0)	18 (41.9)		172 (49.0)
(Sub)total colectomy	10 (3.2)	0 (0.0)	.232	10 (2.8)
AJCC T-stage				
T3	283 (90.7)	41 (93.2)		324 (91.0)
T4	29 (9.3)	3 (6.8)	.591	32 (9.0)
Tumor differentation				
Poor	32 (10.3)	4 (9.1)		36 (10.1)
Moderate	260 (83.6)	38 (86.4)		298 (83.9)
Well	12 (3.9)	1 (2.3)		13 (3.7)
Unknown	7 (2.3)	1 (2.3)	.949	8 (2.3)
Lymphovascular invasion				
No	91 (29.3)	12 (27.3)		103 (29.0)
Yes	23 (7.4)	6 (13.6)		29 (8.2)
Unknown	197 (63.3)	26 (59.1)	.368	223 (62.8)
Adjuvant therapy	18 (5.8)	3 (6.8)	.782	21 (5.9)

examining high-risk factors more closely in our cohort of stage II patients we found that these risk factors did not seem to have a significant impact on survival (Figure 2). In our study, we did not find a significant association between the failure to report any of the five factors and overall survival. No difference was found between left-sided colorectal cancer, right-sided colorectal cancer and colorectal cancer on both sides. As depicted in the Kaplan–Meier graphs, no trend towards a difference was visible for any of the risk factors either (Table 2). Age (HR: 1.06, 95%CI 1.03–1.08, $p < .001$) and ASA Class 3 (HR: 3.52, 95%CI 1.19–10.42, $p = .023$) were significantly associated with OS in univariable analysis. In multivariable analysis age (HR: 1.07, 95%CI 1.04–1.10, $p < .001$), moderately (HR: 0.35, 95%CI 0.18–0.70, $p = .003$) and well (HR 0.11, 95%CI 0.01–0.89, $p = .038$) differentiated tumors were significantly associated with OS, after conditional backwards selection of associated variables.

Discussion

Colorectal cancer is currently one of the most common malignancies in the Western world [1]. For colon cancer, tumors are divided into stage I to IV with a subdivision for stage II patients into low- and high-risk patients, based on the factors pT-stage, tumor differentiation grade, LVI, tumor perforation and, most importantly, lymph node metastasis status. In this study, a set of 356 pathology reports was reviewed to determine the accuracy and completeness regarding the five factors used to identify high-risk stage II colon cancers and the impact on clinical management.

In 2007, Quirke et al. suggested three main reasons for the incompleteness of pathology: the ignorance of the importance of certain features for clinical management, the large number of possible prognostic features that could be reported, and the desire to hold on to free text reports [14]. While the first may be overcome by education and routine audit with feedback, the second and third reason requires a standardized minimum set of items that should be reported. Interestingly, in 1998 the Royal College of Pathologists already suggested such a set which included all five factors examined in the current study [15]. The use of proforma reporting for pathology reports on colorectal cancer specimens has been described to increase the completeness of the reports up to 96% [16,17]. Synoptic reporting, in which a prespecified set of items have to be scored before the report can be finalized, has also been described to add to the completeness of pathology reports [18]. The

Table 2. Survival analysis of stage II colon cancer patients.

	Univariable analysis			Multivariable analysis		
Characteristic	HR	95%CI	*p* value	HR	95%CI	*p* value
Age, years (IQR)	1.06	1.03–1.08	<.001	1.07	1.04–1.10	<.001
AJCC T-stage						
T3	Ref	–	–			
T4	0.84	0.36–1.93	.677			
N-stage						
N0	Ref	–	–			
Nx	1.29	0.70–2.39	.414			
Tumor differentiation						
Poor	Ref	–	–	Ref	–	–
Moderate	0.57	0.29–1.11	.097	0.35	0.18–0.70	.003
Well	0.58	0.16–2.11	.409	0.11	0.01–0.89	.038
Lymphovascular invasion						
No	Ref	–	–			
Yes	1.31	0.58–2.97	.522			
Unknown	1.14	0.68–1.93	.617			
Diabetes						
No	Ref	–	–			
Yes	1.25	0.71–2.20	.446			
Colonoscopy						
No	Ref	–	–			
Yes	1.33	0.32–5.42	.694			
ASA class						
1	Ref	–	–			
2	1.60	0.57–4.46	.371			
3	3.52	1.19–10.42	.023			
Type of operation						
Open resection	Ref	–	–			
Laparoscopic resection	1.13	0.72–1.77	.605			
Type of resection						
Left-sided resection	Ref	–	–			
Right-sided resection	1.03	0.65–1.61	.913			
(Sub)total colectomy	0.44	0.06–3.23	.422			
Adjuvant therapy	0.42	0.10–1.71	.224			

increase of LVI reporting in our data after synoptic reporting became mandatory substantiates these earlier observations.

In 2000, the college of American Pathologists published a statement summarizing and categorizing the pathologic prognostic factors and predictive factors in colorectal cancer [19]. The pT category and pN category of the pTNM staging system as well as LVI were categorized in Category I, which included factors definitively proven to be of prognostic import based on evidence from multiple statistically and methodologically well executed published trials. Tumor grade fell into Category IIA, which included factors extensively studied clinically and/or biologically and repeatedly shown to have prognostic and/or predictive value, but has to be validated in statistically robust studies. The importance to mention these tumor characteristics was illustrated by Maughan et al., who reported an association between the failure to report either vascular invasion or peritoneal involvement and overall survival in a large retrospective study of close to 6000 patients [20].

In our cohort, reporting of most high-risk factors in stage II patients was absent in the majority of the pathology reports between 2007 and 2012. However, a difference in OS between patients in whom factors indicating worse prognosis were not reported and those in whom they were absent was not found. Poorly differentiated tumors performed worse than moderately and well differentiated tumors when corrected for age at the time of surgery. Age itself was an independent risk factor as well. The reasons for the lack of predictive value of the other four recognized high-risk factors in our cohort is likely multifactorial. Firstly, this was a prospectively included cohort in which all variables were scored before the individual disease course of patients was known, eliminating potential bias in the scoring of variables. All patients were demographically similar, as they were treated in the same region in the Netherlands. This also limited differences in the quality of health care potentially correlating with the quality of diagnosis.

The use of adjuvant chemotherapy in stage II colon cancer patients remains open for discussion. Current literature does not support the use of adjuvant chemotherapy for all stage II colon cancer patients since it does not improve disease-free or overall survival as illustrated in the MOSAIC trial [21]. However, the indirect evidence of the beneficial role of adjuvant chemotherapy in stage III colon cancer patients and the identification of high-risk stage II colon cancer patients using the currently available risk factors justifies the consideration of the adjuvant chemotherapy as stated by

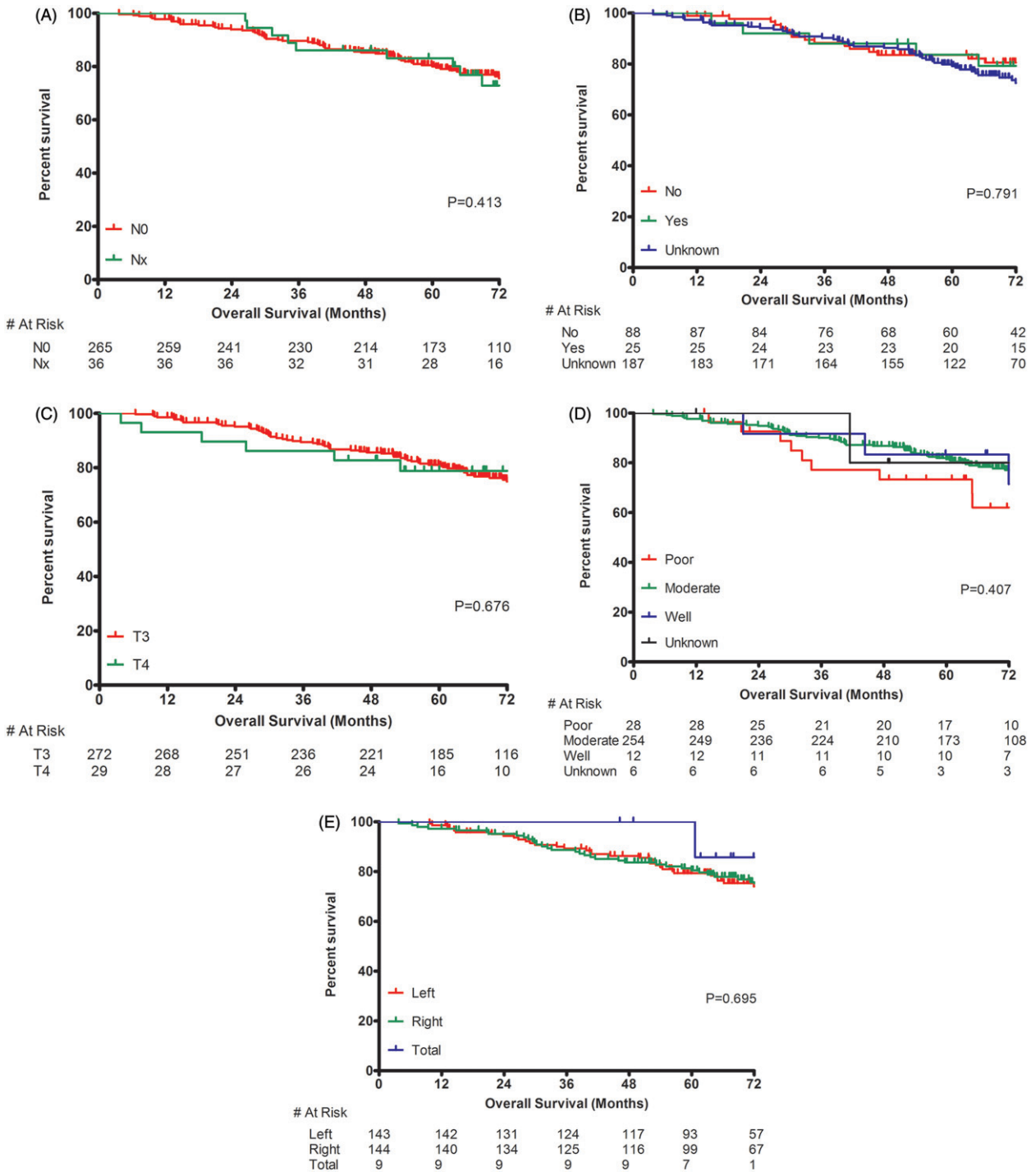

Figure 2. (A) Overall survival stratified by N-stage. (B) Overall survival stratified by T-stage. (C) Overall survival stratified by lymphovascular invasion. (D) Overall survival stratified by differentiation grade. (E) Overall survival stratified by type of colectomy.

the American Society of Clinical Oncology [9]. In our study, the use of adjuvant chemotherapy was not a significant predictor of better overall survival (HR: 0.42, 95%CI: 0.10–1.71, $p = .224$).

Although it is, to our knowledge, the first study into the completeness of prognostic factor reporting in type II colon cancer patients, this study has a number of limitations. First of all, our number of patients is comparatively low. Because our study is based on primary data of patients with stage II colon cancer, however, this is one of the larger studies of its kind [6,14–16]. A direct consequence of cohort size is a relatively low number of patients within some subgroups of the survival analysis. Since selection bias is highly unlikely due to the prospective inclusion of this cohort, we have no reason to question the accuracy of our data. An increase in patient numbers, therefore, would only lead to improved precision (i.e. smaller confidence intervals) and would not change the trends in

survival depicted by our data. We therefore believe that an increase of the number of patients in the subgroups would still not lead us to conclude clinically significant differences over these subgroups, with regard to overall survival.

We conclude that pathology reports should better describe the five high-risk factors in stage II colon cancer, in order to enable proper patient selection for further treatment. Of the five factors, only the tumor differentiation grade was observed to be prognostic in multivariable survival analysis. Chemotherapy may be offered to patients only in select instances, when a certain set of prognostic markers is present. Further research into these prognostic markers is warranted, as a definitive set is still unavailable.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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