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LETTER TO THE EDITOR

An easily adaptable validated risk score predicts cancer-specific survival in stage II colon cancer

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Introduction

High-risk stage II colon cancer is defined in European and American guidelines as the presence of at least one of the following high-risk factors: T4 stage, tumor differentiation grade 3, bowel obstruction or perforation, presence of lymphovascular invasion (LVI), or <12 investigated lymph nodes [1–3]. Perineural invasion (PNI), high tumor budding and compromised surgical margin are also strong predictors of disease recurrence [3–6]. Circulating tumor DNA is a promising novel biomarker in colorectal cancer (CRC) and could be the most influential prognostic marker after radical surgery, but its predictive value has not yet been established [7–9].

A disease-free survival benefit from fluoropyrimidine-based adjuvant chemotherapy in stage II colon cancer has been demonstrated in the Quasar trial [10] and in systematic reviews, with an OS benefit in some [10,11] but not statistically significant in all [12–14]. However, the inclusion and definition of high-risk stage II patients varies between studies and thus also the efficacy. Patients with stage II CRC harboring high microsatellite instability (MSI) show a good prognosis compared to patients with proficient mismatch repair and do not benefit from fluoropyrimidine-based adjuvant chemotherapy [12,15].

Several studies on stage II colon cancer have shown that each of these high-risk factors has a distinct impact on survival, and the relapse risk rises with the number of high-risk factors [16–19]. The relative benefit of adjuvant chemotherapy also varies depending on the high-risk factor [18–20].

Our aim was to assess the significance of each high-risk factor in stage II colon cancer and to develop an easily adaptable risk score, which could predict cancer-specific survival (CSS), with or without adjuvant chemotherapy.

Material and methods

Ethics

Auria Biobank and Clinical Informatics collects tissue samples and clinical data from patients treated at the Turku University Hospital and Satakunta Central Hospital districts in Finland. An independent validation cohort was obtained from the data registry at the department of oncology at Tampere University Hospital. Both Auria and Tampere obtain clinical data directly from operational electronic health record systems. The current study was approved by the Scientific Steering Committee of Auria Biobank, and research permission was granted by the Institutional Review Boards of Turku, Satakunta and Tampere hospitals.

Study population

All patients diagnosed with CRC during 2004–2017 in Turku University Hospital and during 2004–2012 in Satakunta Central Hospital were identified as described earlier [21]. The validation cohort from Tampere was obtained differently, including all patients diagnosed with CRC who were referred to the department of Oncology during 2010–2018. pStage II colon cancers were identified according to the TNM 2010 system, excluding 65 patients with known MSI or OS <1 month. MSI immunohistochemistry was widely implemented in Turku region starting from 2015. R1 resection was defined as proximal, lateral or distal margin of ≤1mm. Right-

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sided colon cancer included tumors from the cecum to the transversal colon and left-sided from the splenic flexure to the sigmoid colon. Patients were classified having 0, 1 or 2+ comorbidities according to Charlson comorbidity classification [22], using hospital ICD-10 codes.

Adjuvant chemotherapy data were available for Turku and Tampere cohorts. By our definition adjuvant therapy was considered given if at least three months of fluoropyrimidine- and/or oxaliplatin-based chemotherapy was completed.

Developing the risk score

An experimental risk score (RS) was created by the authors for stage II colon cancer. First, univariable Cox regression analysis for CSS was performed for each of the high-risk factors present: T4 stage, obstruction/perforation, <12 lymph nodes investigated, grade 3 tumor, R1 resection and presence of LVI and/or PNI. The electronic system reports LVI/PNI as either positive or negative and cannot distinguish between them. Second, since it has been shown that each high-risk factor affects survival in different magnitude [17–20], each high-risk factor was weighted based on Cox hazard ratio (HR), modified from the method used by Charlson [22]: Non-significant factors yield 0 points. Factors with HR 1.5–2.49 yield 1 point, factors with HR 2.5–3.49 yield 2 points, and those with HR 3.5 or more 4 points. These points are added together to calculate the RS. Third, RS was compared to the traditional practice where each high-risk factor yields 1 point [16].

Statistics

The primary endpoint was CSS, defined as the period from diagnosis by a pathologist to date of death due to CRC (ICD10 codes C18–C20) or censored at the end of the follow-up in December 2018 or at time of non-CRC death. Date and cause of death was verified from Statistics Finland, an independent national statistical registry.

The HRs were analyzed with Cox regression using the enter method with 95% confidence interval (CI). High-risk factors with a p-value of <.05 were included in the RS model. The variances were analyzed either with Tukey's ANOVA or Pearson's chi-square test. Area under the receiver-operator curve (AUC or AUROC) was calculated assuming a positive correlation with high RS and short CSS. Survival estimates were calculated with the Kaplan-Meier log-rank method. All statistical analyses were performed with SPSS Statistics version 26 (IBM, Chicago, IL) software.

Results

Study population

Patients with pStage II colon cancer from Turku ($N = 485$) and Satakunta ($N = 219$) cohorts were used for model training. A separate Tampere cohort with 183 pStage II colon cancer patients was used for model validation (Table 1). The median follow-up time was 5.9 years in the training cohort and 3.5 years in the validation cohort. Patients in the validation cohort were younger ($p < .001$) and had received more adjuvant chemotherapy ($p = .006$). LVI/PNI was not routinely assessed in Satakunta cohort (Table 1).

Risk score predicts cancer-specific survival in stage II Colon cancer

In the training cohort, a T4 tumor, presence of LVI/PNI, tumor obstruction or perforation, <12 lymph nodes investigated and R1 resection were negatively associated with CSS. Specifically, R1 resection yielded 4 points (HR 9.8 (3.9–24.9), $p < .001$), T4 tumor 2 points (HR 2.6 (1.6–4.2), $p < .001$), obstruction/perforation 2 points (HR 3.0 (2.0–4.7), $p < .001$), inadequate lymph node sampling 1 point (HR 1.8 (1.2–2.7), $p = .006$) and LVI/PNI 1 point (HR 2.0 (1.0–3.9), $p = .04$). Points were added together to form the RS. Tumor grade was not associated with CSS, HR 0.8 (0.6–1.3), and neither was mucinous histology as compared to non-mucinous histology.

A high RS predicted shorter CSS in the training cohort (Figure 1(A,C), AUC 0.72) and in the validation cohort (Figure 1(B,C), AUC 0.69). Median RS in both training and validation cohorts was 1 (range 0–6). For comparison, simply adding

Table 1. Demographics of the stage II colon cancer study populations.

	Training cohort	Validation cohort
Number of patients	704	183
Female	352 (50%)	86 (47%)
Median and mean age (range)	74 and 72 (26–96) years	69 and 69 (35–93) years
Comorbidities present[a]		
0	63%	61%
1	25%	26%
2 or more	12%	13%
Right-sided primary	346 (49%)	101 (55%)
Known microsatellite stability	80	Not available
Adjuvant therapy for at least 3 months	102 out of 485 patients (21%)[b]	57 (30%)
High-risk factors		
T4	99/704 (14%)	76/183 (41%)
Gradus 3	75/689 (11%)	30/149 (20%)
LVI/PNI	88/428 (21%)	101/160 (63%)
<12 lymph nodes dissected	239/703 (35%)	7/153 (5%)
Obstruction/perforation	120/704 (17%)	14/183 (8%)
R1 resection (≤1mm)	7/704 (1%)	4/183 (2%)

[a]According to Charlson comorbidity classification.
[b]Satakunta adjuvant chemotherapy data was not available.

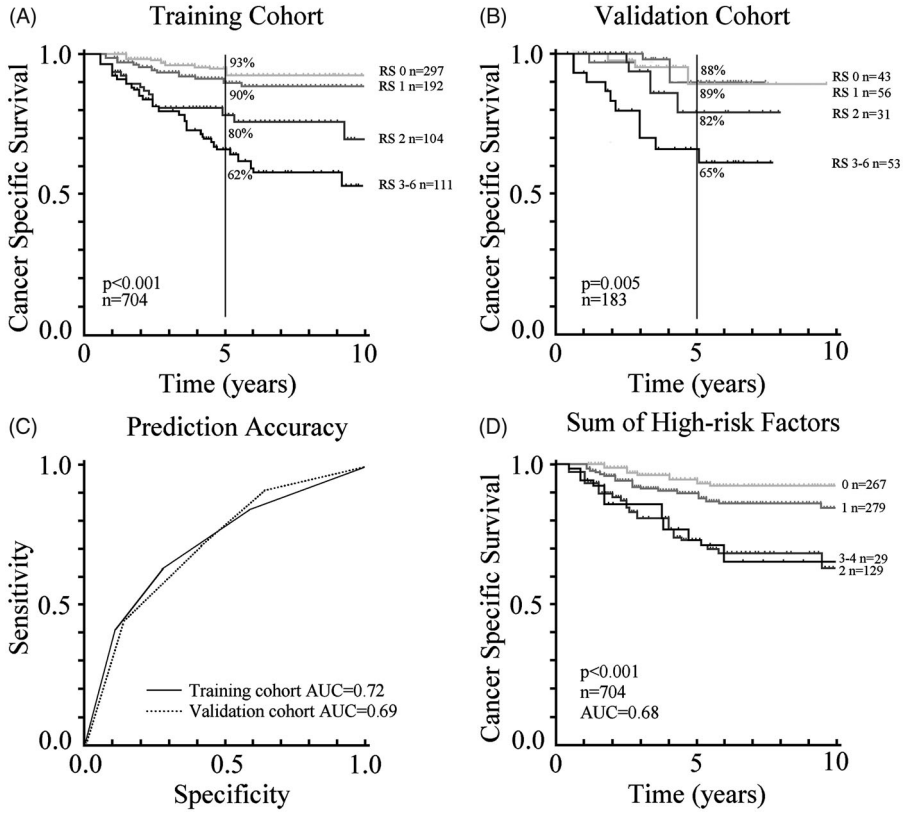

Figure 1. Ten-year cancer-specific survival according to the risk score (RS). (A) Training cohort of 704 patients. (B) Validation cohort of 183 patients. (C) Prediction accuracy of the training and validation cohorts. (D) For comparison, traditional practice using the training cohort, where the number of high-risk factors are added together.

the number of high-risk factors together from the six aforementioned high-risk factors, resulted in an AUC 0.68 in the training cohort, and no CSS difference was observed between patients with 2 or 3+ high-risk factors (Figure 1(D)). Comparing RS 0–1 and 2–6 AUC was 0.68.

To minimize the effect of missing data (Table 1) multivariable analysis was performed (Supplementary Table 1). A T4 tumor, presence of LVI/PNI, lymph node sampling <12 and R1 resection remained as independent prognostic factors, while tumor obstruction/perforation did not. Additionally, gender, presence of comorbidities and tumor location in left or right colon did not affect CSS, but age ≥75 years was independently associated with short CSS (HR 2.5 (1.5–4.3)).

Adjuvant chemotherapy

Patients who had received at least 3 months of chemotherapy and were aged <80 years were pooled from Turku and Tampere cohorts for this analysis ($N = 510$). Overall, in stage II colon cancer CSS did not differ in those who had received adjuvant treatment compared to those who had not (Supplementary Figure 1A). Only in patients with RS 2 or more, a longer CSS was observed in patients who had received adjuvant chemotherapy (HR 0.4 (0.2–0.9), $p = .02$, Supplementary Figure 1B). Those who had received adjuvant chemotherapy were 6 years younger and had less comorbidities.

Discussion

Numerous studies have been conducted to identify which patients with stage II colon cancer are at high risk of recurrence and would benefit from adjuvant chemotherapy, but the definition of high-risk stage II CRC is variable [10–14,17–20]. Our study is in line with previous findings [16–19] showing that a higher number of high-risk factors in stage II colon cancer increases the risk of death from CRC, and we show that this is independent of tumor grade, gender or comorbidities. Here we introduce a RS which can be easily calculated and incorporated into clinical trial design to assess the risk of death from colon cancer.

Disease recurrence nomograms for colon cancer have been developed, but the nomograms include stage II–III patients and rely on complex calculation procedures with AUC values of 0.64–0.77 [23–25] or biomarkers KRAS and BRAF with AUC 0.66–0.74 [26]. Our RS is easy to calculate and has comparable predictive accuracy (0.72) to these models, even though AUC <0.80 is generally considered as limited diagnostic accuracy. CSS was chosen as the primary endpoint, since it could be verified from an independent source and is more precise than OS. The RS performed equally well in both training and validation cohorts, even though the validation cohort was not formally powered and the inclusion criteria for the cohorts were different; the training cohort was biobank-based from consecutively operated CRC patients and the validation cohort included selected patients referred for oncologist for possible adjuvant chemotherapy. This may explain the younger age and higher

frequency of T4 and LVI positive tumors in the validation cohort.

Regular multidisciplinary meetings began during 2004 in Turku region and during 2007 in Tampere region, thus before the current study. In Satakunta the meetings were irregular. At that time in Turku and Satakunta, adjuvant chemotherapy was recommended if at least one of any high-risk factor was present in stage II colon cancer [1], while in Tampere at least two high-risk factors were preferred for adjuvant therapy.

Our study did not support tumor differentiation grade as a prognostic factor for CSS. Similar findings have been reported previously for stage II CRC [7,18,24] while in larger analyses with stage II–III CRCs, tumor grade 3 has remained as a significant prognostic factor [16]. Grading of CRC may be somewhat inconsistent based on known interobserver variation bias, which could affect especially older tumor samples prior to the WHO 2010 classification [27]. This issue has been addressed in the latest 2019 classification where CRC is graded as low or high. The results concerning R1 resection should be interpreted with caution, since some T3R1 tumors may be confused with T4aR0 tumors [6].

It was of great interest to observe how the relative benefit of adjuvant chemotherapy improved as RS increased. CSS benefit from adjuvant therapy was observed only in RS 2–6 patients. Our retrospective study was designed to predict survival with standard adjuvant treatments used in the hospitals of the study, therefore causing selection bias since treatment allocation was not randomized. In the future, new emerging biomarkers including circulating tumor DNA [7–9], could alongside our RS model further improve the tailoring of adjuvant chemotherapy in stage II colon cancer.

In conclusion, our validated RS model predicted survival comparably to other models and nomograms reported previously, without the need for additional biomarkers or complex mathematics. However, due to limited number of patients in the current study, these results should be reproduced in a larger adequately powered prospective study setting. The RS could easily be adapted to clinical trial design by using a structured pathology report.

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Disclosure statement

The authors report no conflicts of interest.

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