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ORIGINAL ARTICLE – COLORECTAL CANCER

High-Risk Stage II Colon Cancer: Not All Risks Are Created Equal

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ABSTRACT

Introduction. Adjuvant chemotherapy is recommended in patients with stage II colon cancer with high-risk features (HRF). However, there is no quantification of the amount of risk conferred by each HRF or the overall survival (OS) benefit gained by chemotherapy based on the risk factor.

Objective. To assess survival benefits associated with adjuvant chemotherapy among stage II colon cancer patients having one or more HRF [T4 tumors, less than 12 lymph nodes examined (< 12LN), positive margins, high-grade tumor, perineural invasion (PNI), and lymphovascular invasion (LVI)].

Methods. Patients diagnosed with stage II colon cancer between 2010 and 2013 were identified from California Cancer Registry. Propensity score weighted all-cause mortality hazard ratios (HR) were calculated for combinations of HRF.

Results. A total of 5160 stage II colon cancer patients were identified, of which 2398 had at least one HRF and 510 of 2398 (21%) received adjuvant chemotherapy. Compared with patients with a single HRF, presence of any 2 or $\geq$ 3 HRF showed increasingly poorer survival [HR 1.42, 95% confidence interval (CI) 1.16–1.73 and HR 2.50, 95% CI 1.96–3.20, respectively]. Chemotherapy was associated with improved overall survival only among patients with T4 as the single HRF (HR 0.51, 95% CI 0.34–0.78) or combinations involving T4 as T4/< 12 LN (HR 0.31, 95% CI 0.11–0.90), T4/high grade (HR 0.26, 95% CI 0.11–0.61), and T4/LVI (HR 0.16, 95% CI 0.04–0.61).

Conclusions. Not all high-risk features have similar adverse effects on OS. T4 tumors and their combination with other HRF achieve the most survival benefit with adjuvant therapy. Type and number of high-risk features should be taken into consideration when recommending adjuvant chemotherapy in stage II colon cancer.

Surgical resection is the mainstay of treatment for stage II colon cancer. Although the benefit of adjuvant chemotherapy has been clearly established in stage III colon cancer, it remains controversial in stage II colon cancer.[1] QUASAR—a randomized, controlled, clinical trial that evaluated the benefit of 5-fluorouracil–based adjuvant chemotherapy in stage I-III colon cancer—failed to demonstrate a survival benefit with adjuvant chemotherapy in stage II colon cancer (relative risk (RR) 0.86, 95% CI 0.66–1.12).[2] Similarly, the International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) reported no significant survival differences between stage II patients treated with adjuvant 5-FU + leucovorin and those treated with surgery alone.[3] Despite lack of definitive evidence, many studies have suggested that a subset of patients with stage II colon cancer with high-risk features (HRF) might achieve improved survival with adjuvant chemotherapy.[4–6] HRF have been defined throughout the literature as T4 tumors, perforation, lymphovascular invasion (LVI), perineural invasion (PNI), less than 12 lymph nodes examined, high-grade tumors, positive margins, and obstruction.[7–10] The American Society of Clinical Oncology, despite the lack of conclusive evidence, recommends consideration of adjuvant chemotherapy in stage II patients with T4 tumors, inadequate lymph node sampling, perforation, or poorly

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differentiated histology.[8] There are several conflicting reports about the benefits of adjuvant chemotherapy even among high-risk patients. The authors of a recent National Cancer Database (NCDB)-based retrospective study of 153,110 patients with stage II colon cancer surmised that there was a statistically significant overall survival benefit with adjuvant chemotherapy for all high-risk stage II patients regardless of high-risk tumor pathologic features (T4 tumor, poorly differentiated tumors, positive margins, or less than 12 LN examined[5]). On the other hand, a SEER Medicare database study reported no survival benefit with adjuvant chemotherapy in stage II colon cancer patients with poor prognostic features.[11] Despite current controversies, the National Comprehensive Cancer Network guidelines recommend consideration for adjuvant chemotherapy in Stage II colon cancers with HRF.[12]

Most studies that have evaluated the benefit of adjuvant chemotherapy in stage II high-risk colon cancer have often collectively analyzed these patients despite the potential biologic heterogeneity among the various HRF. The risk conferred by each HRF and the benefit of adjuvant chemotherapy conferred based on type of risk factor present are unclear. This ambiguity leads to a substantial degree of subjectivity and variability in treatment selection by clinicians for these patients. Developing individualized treatment strategies should consider the amount of risk conferred by each risk factor present. Several studies have proposed a quantification of risk using hazard ratios, but developing a consensus is difficult due to multiple different end points [overall survival (OS), disease-specific survival, disease-free survival (DFS)] and conflicting results.[6,10,13,14] For example, Quah et al. demonstrated T4 tumors as having the highest hazard for survival (hazard ratio (HR) 2.7; 95% confidence interval (CI) 1.1–6.2), whereas Sato et al. showed no statistically significant difference in overall survival between T3 and T4 tumors.[6,13] Finally, even though the presence of HRF might be associated with adverse prognosis, it may not necessarily translate as a predictor of benefit from adjuvant chemotherapy. Developing a hierarchy among these risk factors is important, but clearly determining how these risk factors (both individual and in combination) respond to adjuvant chemotherapy will give clinicians the evidence needed to offer adjuvant therapy. To this end, we sought to quantify the risks conferred by each HRF and their combinations and to evaluate the survival benefit with adjuvant chemotherapy based on each risk factor.

METHODS

Study Population

California Cancer Registry (CCR) is the state-mandated cancer surveillance program that has collected and maintained data for cancer diagnosis and treatment since 1988. In this study, the records for all patients diagnosed with stage II colon adenocarcinoma from January 2010 through December 2013 were retrieved from the CCR database. International Classification of Diseases anatomic site codes C180 and C182-187 were used to identify patients with colon cancer. Patients with overlapping (C188), unspecified colon location (C189), vermiform appendix (C181), and intestine NOS (C26.0) were excluded from study.[15] Although the 7th edition of the American Joint Committee on Cancer (AJCC) staging rules replaced the 6th edition beginning in 2010, this research used the 6th edition staging rules, ensuring continuity of staging categories throughout the study period. This study was approved by the Loma Linda University Institutional Review Board (No. 59061).

Outcome

Overall survival (OS) was the main outcome in this study and was calculated as the time from surgery to death or last date of study follow-up (December 31, 2014), whichever came first.

Risk Factors

Stage II colon cancers HRF assessed in this study included T4 stage tumors, positive margins, examination of less than 12 lymph nodes, and presence of perineural invasion (PNI +), lymphovascular invasion (LVI +), and poorly/undifferentiated tumors.

Chemotherapy

Data classifying receipt of chemotherapy are limited to yes versus no and do not include duration, regimen (single vs. multi-agent), or type of chemotherapy.

Statistical Analyses

Comparisons of patients and tumor characteristics by chemotherapy receipt status (yes vs. no) were conducted using χ^2 tests for independence. To harmonize differences between treatment groups, a two-phase propensity score adjustment was conducted. Initially, patients and tumor characteristics were used as predictors in a logistic regression to generate high-risk feature propensity scores.

Patients' characteristics included age (continuous), sex (male/female), race/ethnicity (Asian/other, Hispanic, non-Hispanic black, and non-Hispanic white), socioeconomic status (SES) quintile, and year of diagnosis, whereas tumor characteristics included signet ring (yes/no) and mucinous (yes/no) histology types as well as location of the primary tumor (right/left). In the second phase, the inverse of the propensity scores (IPWT) generated in the first phase were used as weights to conduct IPWT-Cox regression analyses and estimated weighted mortality hazards ratios (HRs) for various combinations of HRF. All statistical tests in this study were two-sided, conducted at a significance level of five percent ($\alpha = 0.05$) using SAS software, Version [9.4] of the SAS System for Windows© 2002–2012 (SAS Institute Inc.).

RESULTS

Between 2010 and 2013, 5160 stage II colon cancer patients were identified within the CCR, of which 2374 had at least one HRF; 1614 (68%) had only one, 574 (24%) had two, and 186 (8%) had three or more HRF. Table 1 illustrates the demographics of the high-risk study population stratified by receipt of adjuvant chemotherapy. High-grade tumors (441/1614; 27.3%) and less than 12 LN examined (456/1614; 28.3%) were the most common single HRF (Table 2). Among patients with one or more HRF, 510 (21%) received adjuvant chemotherapy. Factors associated with increased likelihood of receiving chemotherapy were younger age ($p < 0.001$), T4 tumors ($p < 0.001$), number of high-risk features ($p < 0.001$), more than 12 lymph nodes examined ($p = 0.012$), presence of LVI ($p = 0.033$), and left-sided tumors ($p = 0.023$; Table 1). Median follow-up time was 35 months, and median overall survival was 60 months.

The adjusted overall survival hazard ratios for each HRF compared with stage II patients without any HRF are listed in Table 3. T4 tumors were associated with the highest risk for reduced overall survival (HR 2.56; 95% C.I. 2.03–3.21) followed by less than 12 LN examined (HR 1.65; 95% CI 1.34–2.02). There was a cumulative effect of HRF on survival: patients with three or more HRF and two HRF compared with one HRF have a significant decrease in survival (HR 2.50; 95% CI 1.96–3.20 and HR 1.42; 95% CI 1.16–1.74, respectively.)

Table 4 shows the covariates-adjusted overall survival hazard ratios for each HRF based on the receipt of adjuvant chemotherapy. The only individual HRF to show an overall survival benefit from adjuvant chemotherapy was a T4 tumor (HR 0.51; 95% CI 0.34–0.78). Adjuvant chemotherapy was associated with a nonsignificant trend towards improved survival when less than 12 LN examined was the only HRF (HR 0.77, 95% CI 0.50–1.18). Additionally, for those with more than one HRF, only combinations of HRF, including T4 tumors showed a benefit from adjuvant chemotherapy (T4 tumor + < 12 lymph nodes, HR 0.31; 95% CI 0.11–0.90; T4 tumor + poorly/undifferentiated tumor, HR 0.26; 95% CI 0.11–0.61; T4 tumor + LVI, HR 0.16; 95% CI 0.04–0.61). No other combinations of HRF showed a significant survival benefit from adjuvant chemotherapy.

DISCUSSION

Several studies have shown that the benefit of adjuvant chemotherapy among patients with stage II colon cancer is limited to patients with high-risk features. However, most of these studies do not quantify the risk associated with each HRF and the survival benefit conferred by adjuvant chemotherapy based on the HRF. Our study has clearly demonstrated that the mortality risk in patients with stage II high-risk colon cancer varies based on the type of HRF. We found that T4 tumors have the strongest negative impact on survival. Furthermore, the presence of a T4 tumor is the only individual HRF that is benefited by adjuvant chemotherapy. These results are in concert with the outcomes reported by Kumar et al., wherein the authors based on a retrospective review of 1697 patients with high-risk stage II colon cancer showed a 5-year overall survival advantage with adjuvant chemotherapy (75.3% vs. 69.3%; $p < 0.001$) compared with no chemotherapy. This benefit was mainly seen in the subgroup of patients with T4 tumors.[9] Verhoeff et al. reported a significant 3-year survival difference in stage II patients with T4 tumors treated with and without adjuvant chemotherapy (91% vs. 73%).[16]

Positive margins, PNI, and LVI were not associated with statistically significant increased risk of mortality compared with the low-risk patients. Although less than 12 LNs examined was a significant predictor of mortality, its presence as the single HRF was not associated with improved survival with adjuvant chemotherapy. Inadequate lymph node sampling, defined as less than 12 LNs examined, has been included as a HRF, because several studies have shown that in stage II and III patients an increased number of LN examined correlates with an increase in survival.[17–19] In our study, nearly 18% of patients received chemotherapy when less than 12 LNs were examined. This finding reflects a current clinical practice of treating stage II patients with adjuvant chemotherapy solely based on inadequate lymphadenectomy and receives some support from our finding of a nonsignificant trend towards improved survival with adjuvant chemotherapy among patients having less than 12 LNs examined.

TABLE 1 Population characteristics by chemotherapy status for high-risk stage II colon cancer 2010–2013

Population characteristics	No chemotherapy (n = 1864)	Chemotherapy (n = 510)	p value
Age (yr)			<0.001
40–50	130 (55.6%)	104 (44.4%)	
51–65	536 (70.0%)	231 (30.0%)	
66–85	1198 (87.3%)	175 (12.7%)	
Sex			0.819
Male	939 (78.7%)	254 (21.3%)	
Female	925 (78.3%)	256 (21.7%)	
Race/ethnicity			0.054
Asian/other	277 (80.3%)	68 (19.7%)	
Hispanic	380 (75.7%)	122 (24.3%)	
Non-Hispanic black	120 (72.3%)	46 (27.7%)	
Non-Hispanic white	1087 (79.9%)	274 (20.1%)	
Tumor stage			<0.001
T3	1385 (85.3%)	239 (14.7%)	
T4	479 (63.9%)	271 (36.1%)	
Lymphadenectomy			0.012
< 12 LN	567 (81.8%)	126 (18.2%)	
≥12 LN	1297 (77.2%)	384 (22.8%)	
LVI			0.033
No	979 (80.0%)	246 (20.0%)	
Yes	384 (74.3%)	133 (25.7%)	
Unknown	453 (78.2%)	126 (21.8%)	
PNI			0.435
No	1433 (78.0%)	404 (22.0%)	
Yes	196 (78.7%)	52 (21.3%)	
Unknown	235 (81.3%)	54 (18.7%)	
Grade			0.638
I (well differentiated)	85 (73.3%)	31 (26.7%)	
II (moderately differentiated)	1096 (78.6%)	298 (21.4%)	
III (poorly/undifferentiated)	664 (79.0%)	176 (21.0%)	
Unknown	19 (79.2%)	5 (20.8%)	
Margins			
Negative	864 (79.3%)	225 (20.7%)	0.334
Positive	604 (76.7%)	183 (23.3%)	
Unknown	396 (79.5%)	102 (20.5%)	
# High-risk Features			
One	1344 (83.3%)	270 (16.7%)	<0.001
Two	404 (70.4%)	170 (29.6%)	
Three or more	116 (62.4%)	70 (37.6%)	
Signet ring			
No	1840 (78.6%)	500 (21.4%)	0.095
Yes	24 (70.6%)	10 (29.4%)	
Mucinous			
No	1685 (78.9%)	451 (21.1%)	0.191
Yes	179 (75.2%)	59 (24.8%)	
Location			
Left-sided	687 (76.1%)	216 (23.9%)	0.023
Right-sided	1177 (80.0%)	294 (20.0%)	

LN lymph nodes, *LVI* lymphovascular invasion, *PNI* perineural invasion

TABLE 2 Frequency and distribution of single HRF (n = 1614)

Feature	n (%)
< 12 LN	456 (28.25%)
High grade	441 (27.32%)
T4	312 (19.33%)
LVI	188 (11.65%)
Positive margin	117 (7.25%)
PNI	100 (6.20%)

HRF high-risk feature, *LN* lymph nodes, *LVI* lymphovascular invasion, *PNI* perineural invasion

TABLE 3 Adjusted overall mortality hazard ratios for each HRF compared to stage II patients without any HRF among patients who did not receive adjuvant chemotherapy

HRF	HR	95% CI
T4	2.56	2.03–3.21
< 12 LN examined	1.65	1.34–2.02
Positive margin	1.31	0.90–1.91
PNI	1.04	0.66–1.63
LVI	0.83	0.57–1.21
High grade	0.84	0.65–1.08

HRF high-risk feature, *LN* lymph nodes, *LVI* lymphovascular invasion, *PNI* perineural invasion

TABLE 4 Covariates-adjusted overall mortality hazard ratios based upon receipt of adjuvant chemotherapy

High-risk feature	HR	95% CI
One feature		
T4 tumor	0.51	0.34–0.78
< 12 lymph nodes	0.77	0.50–1.18
Positive margins	2.37	0.91–6.17
PNI present	1.26	1.05–1.50
LVI present	1.29	1.08–1.54
Poorly/undifferentiated tumor	1.26	1.07–1.50
Two features		
T4 tumor + < 12 lymph nodes	0.31	0.11–0.90
T4 tumor + poorly/undifferentiated tumor	0.26	0.11–0.61
T4 tumor + LVI present	0.16	0.04–0.61

HRF high-risk feature, *LN* lymph nodes, *LVI* lymphovascular invasion, *PNI* perineural invasion

Table 5 summarizes three retrospective studies that have analyzed the effect of adjuvant chemotherapy on survival based on the HRF present in stage II colon cancer patients. The results of our study are similar to that reported by Verhoeff et al., wherein the investigators found that the benefit of adjuvant chemotherapy is limited to patients with T4 tumors (HR 0.43; 95% CI 0.28–0.66), and the benefit of adjuvant chemotherapy in patients with inadequate lymph node evaluation was inconclusive (HR 0.87; 95% CI 0.52–1.46).[16] Kumar et al. reported an overall survival benefit in T4 tumors (HR 0.50; 95% CI 0.33–0.77), LVI (HR 0.46; 95% CI 0.25–0.86), and in less than 12 LNs examined (HR 0.57; 95% CI 0.41–0.81) groups. However, in their study, adjuvant chemotherapy improved disease-specific and recurrence-free survival only in patients with T4 tumors and not in the less than 12 LNs examined or the LVI groups.[9] On the contrary, Casadaban et al., in a large NCDB study, reported that all patients with stage II colon cancer benefit from adjuvant chemotherapy regardless of age or high-risk pathologic features.[5] One of the major issues with the NCDB study was that the unadjusted overall 5-year survival of patients with stage II colon cancer treated by surgery alone was 65.3%, which is much lower than the survival reported by prospective studies.[3,20,21] Hence, the reported benefit with adjuvant chemotherapy for all patients with stage II colon cancer in this study is debatable. We found evidence for improved OS for patients with T4 tumors, combinations of T4 tumors with less than 12 LNs examined, high-grade tumors, or LVI among patients who received adjuvant chemotherapy.

There are certain limitations to our study. Information on certain HRFs, such as clinical presentation with obstruction or perforation, was beyond the scope of information in CCR and hence were not included in the analysis. Microsatellite instability (MSI) status also was unknown in the majority of the patients. High frequency of MSI (MSI-H) is a predictor of better prognosis and could have affected the adjuvant chemotherapy decision. Specifically, the interaction of MSI status and grade and its influence on the effect of adjuvant chemotherapy cannot be discerned by our study. Details about the duration of chemotherapy are not available in CCR; the analysis was primarily based on receipt of any chemotherapy and does not account for early discontinuation of prescribed treatment, which possibly could impact the survival benefit. Additionally, the type of chemotherapy regimen (single vs. multi-agent) administered was not included in the analysis.

Our study has provided valuable information about the relative mortality risk of each HRF in patients with stage II colon cancer. The survival benefit conferred by adjuvant chemotherapy was limited to T4 disease and its combinations with other HRF, such as less than 12 LN examined, LVI, and grade. We believe that these results can aid clinicians with adjuvant treatment decisions in high-risk stage II colon cancer. In the future, customized treatment

TABLE 5 Overall survival hazard ratios with 95% confidence intervals based on individual HRF and the receipt of adjuvant chemotherapy as reported in previous studies

	T4 tumor	< 12 LN	+ margin	LVI	PNI	High grade
Casadaban, et al.[5]	0.75 (0.69–0.82)	0.79 (0.70–0.86)	0.89 (0.78–1.00)	n/a	n/a	0.79 (0.70–0.88)
Kumar, et al.[9]	0.50 (0.33–0.77)	0.57 (0.41–0.81)	n/a	0.46 (0.25–0.86)	0.52 (0.25–1.08)	0.66 (0.35–1.23)
Verhoeff, et al.[16a]	0.43 (0.28–0.66)	0.87 (0.52–1.46)	n/a	n/a	n/a	0.60 (0.22–1.66)

[a]Inadequate LN were considered as < 10 LNs evaluated

decisions based on molecular analysis and gene assays of the tumor will help to eliminate the ambiguity associated with the treatment of these patients.

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