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Combining tumor deposits with the number of lymph node metastases to improve the prognostic accuracy in stage III colon cancer: a post hoc analysis of CALGB/SWOG 80702 phase III study (Alliance)

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ABSTRACT

Background: In colon cancer, tumor deposits (TD) are considered in assigning prognosis and staging only in the absence of lymph node metastasis (i.e., stage III pN1c tumors). We aimed at evaluating the prognostic value of the presence and the number of TD in patients with stage III colon cancer.

Patients and methods: All participants from the CALGB/SWOG 80702 phase III trial were included in this *post hoc* analysis. Pathology reports were reviewed for the presence and the number of TD, lymphovascular and perineural invasion. Associations with disease-free survival (DFS) and overall survival (OS) were evaluated by multivariable Cox models adjusting for gender, treatment arm, T-stage, N-stage, lymphovascular invasion, perineural invasion and lymph node ratio.

Results: Overall, 2028 patients were included, with 524 (26%) TD-positive and 1504 (74%) TD-negative tumors. Of the TD-positive patients, 80 (15.4%) were node negative (i.e., pN1c), 239 (46.1%) were pN1a/b (<4 positive lymph nodes) and 200 (38.6%) were pN2 (≥4 positive lymph nodes). The presence of TD was associated with poorer DFS (adjusted hazard ratio (aHR)= 1.63, 95%CI 1.33-1.98) and OS (aHR = 1.59, 95%CI 1.24-2.04). The negative effect of TD was observed for both pN1a/b and pN2 groups. Among TD-positive patients, the number of TD had a linear negative effect on DFS and OS. Combining TD and the number of lymph node metastases, 104 of 1470 (7.1%) pN1 patients were re-staged as pN2, with worse outcomes than patients confirmed as pN1 (3-year DFS rate: 80.5% *versus* 65.4%, P=.0003; 5-year OS rate: 87.9% *versus* 69.1%, P=<0.0001). DFS was not different between patients re-staged as pN2 and those initially staged as pN2 (3-year DFS rate: 62.3% *versus* 65.4%, P=.4895).

Conclusions: Combining the number of TD and the number of lymph node metastases improved the prognostication accuracy of TNM staging.

KEYWORDS

Colorectal cancer; stage III; adjuvant; tumor deposit; prognosis

HIGHLIGHTS

- Tumor deposits are observed in one fourth of stage III colon cancers.

- Tumor deposits are associated with worse prognosis in stage III colon cancer, regardless of the lymph node substage.

- Tumor deposits should be considered as a quantitative parameter since their number has a prognostic impact.

- Adding the number of tumor deposits to the count of lymph node metastases improves the prognostication accuracy.

INTRODUCTION

The TNM (Tumor Node Metastasis) staging system is the foundation of prognostication and individualized therapeutic strategies in colon cancer. However, variability in survival outcomes exists, especially among stage III colon cancer patients [1]. Although 3 months of adjuvant oxaliplatin-based treatment was not proven to be statistically non-inferior to 6 months, results from the IDEA collaboration allowed for a shortened duration of adjuvant therapy with 3 months of CAPOX, depending on the level of risk [2,3]. Therefore, there is a need to improve the prognostic accuracy for stage III colon cancer patients with seemingly similar TNM substage.

In the 7th version of the AJCC/TNM classification, tumor deposits are defined as discrete tumor nodules of any shape, contour or size that lack associated lymph node tissue, vascular structures or neural structures, found within the lymph drainage area of the primary tumor. Noteworthy, tumor nodules with histological aspects of venous emboli, lymphatic emboli, or perineural invasion are no longer considered as tumor deposits, but as venous emboli, lymphatic emboli, or perineural invasion, respectively, in the 8th version of the AJCC TNM classification. Tumor deposits are observed in approximately 20% of colon cancers [4]. In the absence of lymph node metastasis, presence of tumor deposits is classified as stage III pN1c. In cases with lymph node metastases, neither the presence of tumor deposits nor their number are included in the TNM staging system, despite the finding that tumor deposits have been associated with worse prognosis, regardless of the lymph node stage [4–10]. A post hoc analysis of the IDEA France study showed a deleterious effect of tumor deposits in both N1a/b or N2 patients, with 3-year disease-free survival (DFS) rates of 66.2% and 79.5% for pN1a/b patients with and without tumor deposits, and 50.2% and 60.0% for pN2 patients with and without tumor deposits, respectively. When combining tumor deposits with the number of lymph node metastases, patients initially pN1 and restaged as pN2 (n=35, 2.4%) had similar DFS compared to those

initially classified as pN2 [11]. Therefore, ignoring tumor deposits in the presence of lymph node metastases represents a significant loss of prognostication accuracy, currently with even greater importance since the count of lymph node metastases now guides therapeutic decision regarding the duration and the type of adjuvant chemotherapy [2]. The potentially practice-changing results of the IDEA France study require validation, particularly as most pathology reports in this study lacked standardization [12].

In the Cancer and Leukemia Group B/Southwest Oncology Group (CALGB/SWOG) 80702 phase III study (NCT01150045), 2,526 stage III colon cancer patients were randomized to 3 *versus* 6 months of adjuvant FOLFOX plus 3 years of celecoxib or placebo. The primary objective was to compare DFS of patients treated with standard chemotherapy with or without celecoxib. CALGB is now part of the Alliance for Clinical Trials in Oncology. Here, we evaluated the prognostic value of tumor deposits for predicting DFS and overall survival (OS), and the impact of combining tumor deposits with the number of lymph node metastases in patients with stage III colon cancer treated on the CALGB/SWOG 80702 phase III trial.

MATERIAL AND METHODS

Patients

CALGB/SWOG 80702 was a phase III trial with a 2 x 2 factorial randomization between 6 or 12 cycles of FOLFOX and 3 years of celecoxib or placebo (double-blind) for patients with stage III colon cancer. The main eligibility criteria were histologically documented adenocarcinoma, complete resection (R0), at least one positive lymph node metastases or N1c disease as defined in AJCC version 7 [13], no evidence of metastatic disease, no neurosensory or neuromotor toxicity ≥ grade 2, and Eastern Cooperative Oncology Group (ECOG) performance status 0-2. Results for the primary end point (DFS) have been previously reported [14]. Each

participant signed an IRB-approved, protocol-specific informed consent document in accordance with federal and institutional guidelines.

In this post hoc analysis, pathology reports from all patients were reviewed by one physician (RC or ZJ) for the presence and count of tumor deposits, as well as for the primary tumor sidedness, the presence of lymphovascular or perineural invasion. Data from pathology reports with no specific mention of either the presence or the absence of tumor deposits were considered as missing. For cases without a recorded number of tumor deposits, a value of 2 was assigned when multiplicity was indicated and a value of 1 was assigned in other cases. Tumors arising in the splenic flexure, descending colon, sigmoid or upper rectum were classified as left-sided; those originating in cecum, ascending colon, hepatic flexure or transverse colon were classified as right-sided.

Objectives

The outcomes included DFS, defined as the time from date of randomization to documentation of disease recurrence or death due to any cause and OS, defined as the time from randomization to death from any cause. A second primary colorectal cancer was not considered a DFS event. The pN stage was recalculated by combining the number of tumor deposits with the number of lymph node metastases.

Statistical analysis

The data for this analysis was frozen on April 20th 2020. Survival curves were estimated using the Kaplan-Meier method with adjustment for gender, treatment arm, T-stage, N-stage, lymphovascular invasion, perineural invasion and lymph node ratio, and compared with a likelihood ratio test [15–17]. Follow-up was calculated by reverse Kaplan-Meier estimation. Cox proportional hazard models were performed to estimate hazard ratio (HR) and 95% confidence interval (95%CI) for factors associated with DFS and OS [18]. The association of baseline

parameters with DFS and OS was first assessed using univariable Cox analyses, parameters with P-values < 0.05 were then entered into a final multivariable Cox regression model after considering collinearity among variables with a correlation matrix.

Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies.

RESULTS

Patient characteristics

Among 2526 patients included in the CALGB/SWOG 80702 trial, 498 (19.7%) were excluded from the present analysis: two stage 4 patients, 34 without available pathology reports, and 462 without specific information concerning the presence or absence of tumor deposits. Overall, 2028 patients were included in the analysis, with 524 (26%) tumor deposit-positive and 1504 (74%) tumor deposit-negative stage III colon cancers (supplementary figure 1).

Baseline characteristics according to the presence or the absence of tumor deposits are summarized in table 1. Eighty patients (3.9%) had pN1c tumor (presence of tumor deposits but no lymph node metastasis). Seventeen point two percent and 37.0% of pN1a/b and pN2 tumors, respectively, had tumor deposits. Patients with tumor deposits were more likely to have T4 or N2 tumors with lymphovascular invasion and perineural invasion (P<.0001).

Prognostic value of the presence of tumor deposits

The median overall follow-up was 5.8 years (95%CI 5.8-5.9). The 3-year DFS and 5-year OS estimates of pN1a/b, pN1c and pN2 groups were 79.4%, 79.6%, 62.3%, and 86.6%, 85.9%, 74.1%, respectively (supplementary figure 2). Patients with pN1c tumors did not have different outcomes to that of the pN1a/b population (unadjusted HR = 1.03, 95%CI 0.61-1.74).

The presence of tumor deposits was associated with poorer DFS (HR = 1.63, 95%CI 1.33-1.98, p=<.0001) and OS (HR = 1.59, 95%CI 1.24-2.04, p=0.0004) in the overall population (supplementary figure 3). The negative effect of tumor deposits on DFS and OS was observed for both pN1a/b and pN2 groups (figure 1A and 1B). 3-year DFS rates for pN1a/b patients with or without tumor deposits were respectively 70.2% (95%CI 65.8-74.8) *versus* 81.4% (79.6-83.2); 5-year OS rates were 79.5% (75.6-83.7) *versus* 88.1% (86.6-89.6). For pN2 patients with or without tumor deposits, 3-year DFS estimates were 53.7% (48.5-59.4) *versus* 67.1% (63.3-71.0), and 5-year OS rates were 67.2% (62.3-72.5) *versus* 77.9% (74.6-81.4). The effect of tumor deposits on DFS was consistent in all clinical subgroups (figure 2). No interaction between tumor deposits and lymphovascular or perineural invasion was observed (P=.599 and P=.990, respectively). The interaction between tumor deposits and treatment arm did not reach statistical significance after Bonferroni multiplicity adjustment.

In a univariable Cox model, the presence of tumor deposits was associated with poor DFS (HR = 1.85; 95%CI 1.56-2.20) and OS (HR = 1.91, 95%CI 1.54-2.37). Other variables significantly associated with DFS (supplementary table 1) and OS (supplementary table 2) were: age (OS only), gender, performance status (OS only), primary tumor sidedness (OS only), T-stage, N-stage, TN stage, lymph node ratio, lymphovascular invasion and perineural invasion. In a multivariable Cox model including tumor deposits, gender, T-stage, N-stage, lymph node ratio, lymphovascular invasion, and perineural invasion, the presence of tumor deposits was associated with significantly poorer DFS (HR = 1.63, 95%CI 1.33-1.98) and OS (HR = 1.59, 95%CI 1.24-2.04).

Effect of adding number of tumor deposits to number of lymph node metastases

The median number of tumor deposits was two. Among these, the number of tumor deposits had a linear effect on DFS and OS, with increased number of tumor deposits associated

with a significant increase in the HR for DFS or OS (figure 3A, supplementary figure 4 and supplementary figure 5A).

Given its additive prognostic value, the number of tumor deposits was combined with the number of lymph node metastases, and by doing this 104 of 1470 (7.1%) patients initially considered as pN1 were re-staged as pN2. Compared to patients that remained classified as pN1, re-staged pN2 patients experienced significantly worse DFS (3-year DFS rate: 80.5% *versus* 65.4%, P=.0003) and OS (5-year OS rate: 87.9% *versus* 69.1%, P=.0001) (figure 3B and supplementary figure 5B). DFS was not different between patients re-staged as pN2 and those initially staged as pN2 (3-year DFS rate: 65.4% *versus* 62.3%, respectively, P=.4895; figure 3B). OS survival curves of these two groups crossed, with better outcomes during the first 3 years of follow-up but poorer 5-year estimates for re-staged pN2 patients (5-year OS rate: 74.0% *versus* 69.0%, P=.1312) (supplementary figure 5B).

When considering the pTN stage (pT1-1-3 and N1, pT4 and/or N2), similar trends were observed, but without statistical significance. Seventy-five low-risk stage III patients (i.e, pT1-3 and pN1) were restaged as high-risk (i.e pT4 and/or N2) by combinig the number of tumor deposits with the number of lymph node metastases, with a 3-year DFS rate of 73.9% (95%CI 66.7-81.8), compared to 82.1% (95%CI 80.4-83.8) for confirmed low-risk patients and 63.3 (95%CI 60.7-66.1) for initially high-risk cases.

DISCUSSION AND CONCLUSION

Tumor deposits in colon cancer tumor specimens are observed in more than one fourth of stage III patients. Patients without lymph node metastases but with tumor deposits (namely the pN1c population) experienced similar outcomes to patients staged as pN1a/b. For patients with one positive lymph node or more, the presence of tumor deposits was associated with

significantly poorer survival outcomes. The number of tumor deposits had a linear effect on prognosis and should therefore be considered as a quantitative variable rather than a qualitative information. Adding the number of tumor deposits to the lymph node metastases count improved the prognostic accuracy of the TNM staging. Patients with tumors initially classified as pN1 (< 4 lymph node metastases) but re-staged as pN2 (tumor deposits + lymph node metastases ≥ 4) had significantly poorer DFS and OS compared to those confirmed as pN1 (tumor deposits + lymph node metastases < 4) and outcomes similar to that of patients with 4 lymph node metastases or more.

A post-hoc analysis of the IDEA France study reported a negative impact of tumor deposits on DFS [12]. The observed frequency of tumor deposits was 9.5%, but may have been artificially low because only 36.7% of pathology reports were standardized to include this information. In our study, the observed frequency of tumor deposits in stage III colon cancer was higher (26%) and more in accordance with the incidence reported in other publications. Eighteen point three percent of the CALGB/SWOG 80702 study population was excluded from this analysis due to lack of standardization of pathology reports, related to missing information about the presence or absence of tumor deposits in pathology reports. Our study, therefore, provides a more accurate estimation of tumor deposit frequency. In the current AJCC TNM staging, tumor deposits are taken into account for 3.9% of stage III colon cancers only (pN1c patients) while they could provide valuable prognostic information for 26% of the entire stage III population.

A recent analysis of the Surveillance, Epidemiology and End Results (SEER) database confirmed the independent prognostic value for reporting tumor deposits in CRC. The authors proposed a new AJCC/TNM classification system incorporating the presence or absence of tumor deposits within the N stage [6]. A similar proposal emerged from a retrospective analysis of the National Cancer Database (NCDB) [10]. Herein, we demonstrate that the number of tumor

deposits has added prognostic significance, which justify considering tumor deposits as a quantitative variable instead of a qualitative value. Adding tumor deposit status to the lymph node metastases count might directly impact 6.6% of stage III colon cancer patients who would be classified as pN1 with the 7th or 8th version of the AJCC staging but, with more than 4 tumor deposits or lymph node metastases, should in fact be considered as pN2. Indeed, their prognosis is significantly poorer than pN1 patients and not different from the prognostic profile of the AJCC pN2 category. Importantly, our study found that even though most pathology reports were standardized for the presence or absence of tumor deposits, the specific count of tumor deposits was reported for only 345 of 524 tumors (65.8%) where tumor deposits were present. We chose a worse-case scenario method by assigning a value of 2 for cases without a specific count but with the notion of tumor deposits plurality, and a value of 1 for cases without any detail about the number of tumor deposits.

Previous publications have suggested a potential pathophysiologic relationship between tumor deposits and lymphovascular or perineural invasion, which are high-risk features of stage II colon cancer [10,12,19]. The IDEA France analysis observed a significant interaction between tumor deposits and these features, but the relatively high amount of missing data did not permit firm conclusions to be drawn [12]. Here, the presence or absence of lymphovascular and perineural invasion was reported for 94.9% of patients. The negative prognostic impact of tumor deposits remained significant whether the tumor exhibited lymphovascular or perineural invasion or not.

Although 3 months of adjuvant therapy is not inferior to a 6-month treatment when using CAPOX for low-risk stage III colon cancer patients, 6 months of FOLFOX is superior to 3 months of FOLFOX for high-risk stage III colon cancer patients [3,20]. As all patients from CALGB/SWOG 80702 study received FOLFOX, we cannot therefore draw conclusions concerning the therapeutic effect in patients originally considered as low-risk who would have

been classified as high-risk when adding tumor deposits to the lymph node metastases count. The final missing piece of information for the implementation of tumor deposits in therapeutic decision-making related to the duration and type of adjuvant treatment is the analysis of tumor deposits in stage III colon cancer patients treated with CAPOX. Unfortunately, such a post hoc analysis may not be feasible since tumor deposits are not yet routinely reported in pathological analyses.

Our study has several limitations. First it relied on an unplanned review of pathology reports, and the original study did not require standardization of pathology reporting or specifically request tumor deposit counts. Our results are supported by the fact that the vast majority of the reports were standardized and therefore relatively trustworthy considering the information about tumor deposits. Nonetheless, we recognize the likely wide variability of reporting tumor deposits. Another potential source of error is that the reports were signed by pathologists from multiple institutions, and the study did not require specific expertise in identification of tumor deposits. This is of importance since the definition of tumor deposits changed with the 7th version of the TNM staging classification which introduced the pN1c category [13]. Given the prognostic impact of tumor deposits, we advocate for a clear, systematic and standardized description of the presence and number of tumor deposits in pathology reports.

In summary, tumor deposits are an independent negative prognostic factor, with a linear relationship between DFS, OS and the number of tumor deposits. Adding tumor deposits to the lymph node metastases count improves the prognostic accuracy of the TNM staging. A modification of the current N classification of the AJCC/TNM staging system is warranted.

Trial registration: Clinicaltrials.gov Identifier: NCT01150045.

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Table 1: Baseline characteristics

| | Tumor Deposits | | | |
	No (N=1504)	Yes (N=524)	Total (N=2028)	P-value
Arm, n (%)				0.6015[1]
FOLFOX + placebo (3 months)	393 (26.1%)	146 (27.9%)	539 (26.6%)	
FOLFOX + celecoxib (3 months)	367 (24.4%)	130 (24.8%)	497 (24.5%)	
FOLFOX + placebo (6 months)	347 (23.1%)	125 (23.9%)	472 (23.3%)	
FOLFOX + celecoxib (6 months)	397 (26.4%)	123 (23.5%)	520 (25.6%)	
Gender, n (%)				0.8855[1]
Female	660 (43.9%)	232 (44.3%)	892 (44.0%)	
Male	843 (56.1%)	292 (55.7%)	1135 (56.0%)	
Missing	1	0	1	
Ethnicity, n (%)				0.1214[1]
Not Hispanic or Latino	1348 (92.0%)	479 (94.1%)	1827 (92.6%)	
Hispanic or Latino	117 (8.0%)	30 (5.9%)	147 (7.4%)	
Missing	39	15	54	
Race, n (%)				0.4997[1]
White	1198 (80.9%)	411 (79.7%)	1609 (80.6%)	
Black or African American	195 (13.2%)	76 (14.7%)	271 (13.6%)	
Asian	60 (4.1%)	15 (2.9%)	75 (3.8%)	
American Indian or Alaskan Native	5 (0.3%)	4 (0.8%)	9 (0.5%)	
Native Hawaiian or Pacific Islander	3 (0.2%)	2 (0.4%)	5 (0.3%)	
Multiple	20 (1.4%)	8 (1.6%)	28 (1.4%)	
Missing	23	8	31	
Age				0.2414[2]
N	1504	524	2028	
Mean (SD)	60.7 (10.80)	61.4 (10.81)	60.9 (10.80)	
Median	61.2	61.3	61.3	
Range	19, 88	26, 84	19, 88	
Age (Grouped), n (%)				0.7211[1]
≤65 years	946 (62.9%)	325 (62.0%)	1271 (62.7%)	
>65 years	558 (37.1%)	199 (38.0%)	757 (37.3%)	
Performance Status, n (%)				0.0772[1]
0	1083 (72.0%)	356 (67.9%)	1439 (71.0%)	
1-2	421 (28.0%)	168 (32.1%)	589 (29.0%)	
T-stage, n (%)				<.0001[1]
T1-3	1283 (86.0%)	407 (78.4%)	1690 (84.0%)	
T4	209 (14.0%)	112 (21.6%)	321 (16.0%)	
Missing	12	5	17	
N-stage, n (%)				<.0001[1]

| | Tumor Deposits | | | |
	No (N=1504)	Yes (N=524)	Total (N=2028)	P-value
N1a/b	1151 (77.2%)	239 (46.1%)	1390 (69.2%)	
N1c	0 (0.0%)	80 (15.4%)	80 (4.0%)	
N2	340 (22.8%)	200 (38.5%)	540 (26.9%)	
Missing	13	5	18	
No. of Examined Lymph Nodes, n (%)				0.0985[1]
<12	92 (6.1%)	43 (8.2%)	135 (6.7%)	
≥12	1412 (93.9%)	481 (91.8%)	1893 (93.3%)	
Lymph Node Ratio				0.0002[2]
N	1484	517	2001	
Mean (SD)	0.13 (0.13)	0.19 (0.20)	0.15 (0.15)	
Median	0.09	0.13	0.09	
Range	0.01, 1.00	0.00, 1.00	0.00, 1.00	
Lymph Node Ratio, n (%)				<.0001[1]
≤0.3	1350 (91.0%)	414 (80.1%)	1764 (88.2%)	
>0.3	134 (9.0%)	103 (19.9%)	237 (11.8%)	
Missing	20	7	27	
Risk Group, n (%)				<.0001[1]
T1-3N1	1003 (67.2%)	259 (49.9%)	1262 (62.8%)	
T4 or N2	489 (32.8%)	260 (50.1%)	749 (37.2%)	
Missing	12	5	17	
Sidedness, n (%)				0.3273[1]
Right-sided	790 (52.8%)	263 (50.3%)	1053 (52.1%)	
Left-sided	707 (47.2%)	260 (49.7%)	967 (47.9%)	
Missing	7	1	8	
Lymphovascular Invasion, n (%)				<.0001[1]
Yes	673 (45.8%)	311 (60.4%)	984 (49.6%)	
No	796 (54.2%)	204 (39.6%)	1000 (50.4%)	
Missing	35	9	44	
Perineural Invasion, n (%)				<.0001[1]
Yes	202 (14.0%)	156 (32.3%)	358 (18.6%)	
No	1240 (86.0%)	327 (67.7%)	1567 (81.4%)	
Missing	62	41	103	
Any Invasion, n (%)				<.0001[1]
Yes	724 (50.1%)	345 (68.9%)	1069 (54.9%)	
No	721 (49.9%)	156 (31.1%)	877 (45.1%)	
Missing	59	23	82	

[1]Chi-Square p-value; [2]Kruskal-Wallis p-value;

FIGURE LEGENDS

Figure 1: Disease-free survival and overall survival in pN1a/b, pN1c and pN2 patients according to the presence or absence of tumor deposits

Figure 2: Forest plot for the effect of tumor deposits on disease-free survival among clinical subgroups

Figure 3: Disease-free survival according to the number of tumor deposits (A) and by pN stage after adding tumor deposits to the count of positive lymph nodes (B)

Tumor Deposits/N-stage	Events/Total	3 year DFS Est (95% CI)
No Tumor Deposits+N1a/b	219/1079	81.4 (79.6-83.2%)
Tumor Deposits+N1a/b	77/221	70.2 (65.8-74.8%)
Tumor Deposits+N1c	15/67	79.6 (73.0-86.8%)
No Tumor Deposits+N2	111/317	67.1 (63.3-71.0%)
Tumor Deposits+N2	89/183	53.7 (48.5-59.4%)

No. at Risk

1079	926	795	696	564	341
221	181	147	125	93	56
67	58	51	43	39	22
317	251	203	167	141	79
183	124	87	70	55	32

Survival adjusted for Treatment, Sex, T-stage, lymphovascular invasion, perineural invasion, and lymph node ratio

Survival adjusted for Treatment, Sex, T-stage, lymphovascular invasion, perineural invasion, and lymph node ratio

Tumor Deposits
Yes vs No

	Events/Total	Hazard Ratio (95% CI)	Interaction P-value
Arm			0.0128
FOLFOX + placebo (3 months)	163/539	2.26 (1.65-3.09)	
FOLFOX + celecoxib (3 months)	142/497	1.20 (0.83-1.73)	
FOLFOX + placebo (6 months)	126/472	1.64 (1.14-2.36)	
FOLFOX + celecoxib (6 months)	130/520	2.54 (1.79-3.62)	
Gender			0.1050
Female	207/892	2.20 (1.67-2.91)	
Male	354/1135	1.67 (1.34-2.09)	
Ethnicity			0.9070
Not Hispanic or Latino	510/1827	1.88 (1.57-2.26)	
Hispanic or Latino	35/147	1.81 (0.85-3.88)	
Race			0.4692
White	443/1609	1.88 (1.54-2.28)	
Black or African American	76/271	2.32 (1.47-3.65)	
Asian	24/75	1.31 (0.52-3.29)	
Age			0.5982
≤65 years	335/1271	1.79 (1.44-2.24)	
>65 years	226/757	1.95 (1.49-2.56)	
Performance Score			0.4066
0	389/1439	1.95 (1.59-2.40)	
1-2	172/589	1.64 (1.20-2.24)	
T-stage			0.9043
T1-3	414/1690	1.75 (1.43-2.15)	
T4	144/321	1.69 (1.21-2.34)	
N-stage			0.5363
N1a/b	316/1390	1.89 (1.47-2.42)	
N2	220/540	1.64 (1.25-2.14)	
No. Lymph Nodes Examined			0.6331
<12	47/135	2.17 (1.22-3.86)	
≥12	514/1893	1.82 (1.52-2.18)	
Lymph Node Ratio			0.4420
≤0.3	437/1764	1.66 (1.36-2.03)	
>0.3	119/237	1.94 (1.34-2.79)	
Risk Group			0.9509
T1-3N1	263/1262	1.68 (1.28-2.19)	
T4 or N2	295/749	1.62 (1.28-2.04)	
Sidedness			0.8652
Left-sided	266/967	1.82 (1.42-2.33)	
Right-sided	294/1053	1.85 (1.46-2.35)	
Lymphovascular Invasion			0.5990
Yes	309/984	1.89 (1.51-2.37)	
No	237/1000	1.72 (1.30-2.27)	
Perineural Invasion			0.9903
Yes	122/358	1.72 (1.21-2.46)	
No	402/1567	1.73 (1.40-2.14)	
Any Invasion			0.2566
Yes	338/1069	1.87 (1.51-2.32)	
No	198/877	1.48 (1.07-2.06)	

Hazard Ratio scale: 0.5   1   2   4

Hazard Ratio

Favors Tumor Deposits ← | → Favors No Tumor Deposits

Survival adjusted for Treatment, Sex, T-stage, lymphovascular invasion, perineural invasion, and lymph node ratio