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Implications of lymph node retrieval in locoregional rectal cancer treated with chemoradiotherapy: A California Cancer Registry Study☆

A. Gill[a], **A. Brunson**[a], **P. Lara Jr.**[a], **V. Khatri**[b], and **T.J. Semrad**[a,*]

[a] Division of Hematology/Oncology, Department of Internal Medicine, University of California, Davis Comprehensive Cancer Center, Sacramento, CA, USA

[b] Division of Surgical Oncology, Department of Surgery, University of California, Davis Comprehensive Cancer Center, Sacramento, CA, USA

Abstract

Background—In contrast to colon cancer, the implications of reduced lymph node retrieval in rectal cancer are unclear.

Methods—Using the California Cancer Registry, we performed a retrospective cohort study of 4790 patients with stage I – III rectal cancer diagnosed from 2000 to 2007 who underwent tri-modality therapy. Using multivariate Cox proportional hazards models adjusted for age, sex, race, socioeconomic status, T-stage, and lymph node numbers, we evaluated rectal cancer specific survival (RC-SS) in neoadjuvant and adjuvant cohorts in the overall population and amongst those without involved lymph nodes (pN0).

Results—Sixty one percent of evaluable patients were treated with neoadjuvant chemoradiation. Although there was no difference in RC-SS between neoadjuvant and adjuvant chemoradiation cohorts, the median number of lymph nodes examined was reduced after neoadjuvant therapy (8 vs. 11, $p < 0.0001$). Positive lymph nodes were associated with worse RC-SS regardless of sequence, although the effect was numerically stronger for residual lymph nodes in the neoadjuvant cohort. Compared to at least 12, eight or fewer lymph nodes retrieved was associated with worse outcome in both neoadjuvant and adjuvant cohorts. However, no association between reduced lymph nodes examined and RC-SS was seen in the neoadjuvant cohort when the analysis was restricted to pN0 patients.

Conclusions—In this large cohort of rectal cancer patients treated with tri-modality therapy, reduced lymph node retrieval in node negative patients did not provide additional prognostic information in patients treated with neoadjuvant therapy.

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* Corresponding author. Division of Hematology/Oncology, Department of Internal Medicine, University of California, Davis, 4501 X Street, Suite 3016, Sacramento, CA 95817, USA. Tel.: +1 916 734 3771; fax: +1 916 734 7946. thomas.semrad@ucdmc.ucdavis.edu (T.J. Semrad)..

Conflict of interest statement

All authors have no conflicts of interest to disclose.

Keywords

Rectal neoplasms; Lymph nodes; Neoadjuvant therapy; Chemoradiotherapy; Adjuvant; Neoplasm staging

Introduction

Approximately 40,000 new cases of rectal cancer are diagnosed in the United States each year.[1] Management of this disease has changed significantly since 2000, when the National Cancer Institute (NCI) revised the surgical treatment guidelines for colorectal cancer.[2] In 2000, locally advanced rectal cancer was frequently managed by primary surgery followed by adjuvant chemoradiotherapy (CRT).[3] However, with the publication of the German Rectal Cancer Study Group (CAO/ARO/AIO-94) trial in 2004, neoadjuvant CRT became the preferred approach for most cases of clinical stage II and III rectal adenocarcinoma.[4]

In the last decade, the impact of increased lymph node retrieval on outcomes of surgically-resected colorectal cancer has been identified in both population-based and clinical studies.[5,6] Guidelines from the American Joint Committee on Cancer (AJCC) and College of American Pathologists (CAP) currently recommend evaluation of a minimum of 12 lymph nodes after colorectal surgery.[7–9] Indeed, removal and pathologic examination of at least 12 regional lymph nodes from resected colon cancer is a National Quality Forum endorsed metric.[10] Since the data supporting this recommendation are derived primarily from studies of patients undergoing surgery for colon cancer, the extent to which this measure should be extrapolated to rectal cancer is not clear.

While lymph node retrieval may be altered by surgical procedure and the intensity of pathologic examination, other predictors of lymph node retrieval in colorectal cancer include age, gender, and tumor site.[11] Additionally, recent studies demonstrate that fewer total lymph nodes are recovered after CRT and that only a fraction of specimens contain adequate lymph nodes after neoadjuvant CRT for rectal cancer.[11–15] Nonetheless, studies have come to conflicting conclusions as to whether increased lymph node retrieval is associated with outcome after neoadjuvant CRT.[12–19]

Given that lymph node examination has had important implications on patient prognosis and because lymph nodes status may influence decisions regarding adjuvant therapy and intensity of follow up, we sought to evaluate the prognostic implications of lymph node retrieval and examination in rectal cancer treated with neoadjuvant CRT in a contemporary large population-based study.

Patients and methods

Setting and subjects

We conducted a retrospective cohort study using the California Cancer Registry (CCR), a statewide, population-based cancer registry. The registry includes demographic, diagnostic, treatment and outcome information. To ensure current follow up for vital status and cause of death, the CCR database is linked annually to death certificates, hospital discharge data,

Medicare files, and the National Death Index. For patients diagnosed since 2000, follow up is over 95%.

Patients were included in this study if they were 18 years of age or older; diagnosed with stage I, II, or III rectal cancer between the years 2000 and 2007; and underwent tri-modality therapy consisting of surgery, chemotherapy, and radiation (Fig. 1). Surgery is defined by the CCR as the operation performed on the primary tumor site within the first 6 months of diagnosis. Because our intention was to evaluate the outcome of patients who actually underwent the specified treatment, we did not attempt to impute missing data.

Patients were excluded if they had a prior history of cancer, unknown cause of death, or if there was missing data regarding stage, treatment, lymph node number, or survival. Based on the radiation treatment sequence code (RADSEQ) from the CCR database, patients were divided into two cohorts: those who received chemotherapy and radiation prior to surgery (neoadjuvant CRT), and those who underwent surgery followed by adjuvant chemotherapy and radiation.

Primary outcome

The primary outcome was rectal cancer specific survival (RC-SS), which was defined as the time from diagnosis until death due to rectal cancer or December 31, 2008.

Covariates

Age, sex, race, socioeconomic status (SES), T-stage, number of positive lymph nodes, and number of examined lymph nodes were obtained from relevant registry fields. Regional lymph node data are extracted from the pathology reports by the reporting institution. After visualization of the distribution of lymph nodes retrieved, this variable was categorized as 0–2, 3–5, 6–8, 9–11, and 12 or more.

Statistical analysis

Baseline characteristics of the two cohorts were compared using the Chi-squared test. Multivariate Cox proportional hazards models adjusting for covariates were constructed for the entire population and then repeated for the subset of pathologic node negative patients. The Kaplan–Meier method was used to construct survival curves for RC-SS comparing the neoadjuvant and adjuvant cohorts. Analyses were repeated for overall survival, which may be more impacted than RC-SS by factors beyond initial treatment. However, the results for overall survival were not significantly different, and RC-SS results are reported. Two-sided P values less than 0.05 were considered statistically significant. All statistical analysis was performed using SAS software version 9.3 (SAS Inc., Cary, NC, USA). This study was approved by the University of California, Davis Institutional Review Board.

Results

We identified 8946 patients who were diagnosed with stage I – III rectal cancer between 2000 and 2007 (Fig. 1). Of these, 4790 underwent tri-modality therapy consisting of surgery, chemotherapy, and radiation. We excluded a further 175 patients for having an unknown

cause of death. Within the eligible population, 2833 patients (61%) underwent CRT prior to surgery (the neoadjuvant cohort) and 1782 patients (39%) proceeded to surgery before receiving adjuvant CRT (the adjuvant cohort).

Baseline characteristics of the two cohorts are presented in Table 1. Median age at diagnosis was 59 in the neoadjuvant cohort and 62 in the adjuvant cohort. There was an approximate 3:2 male predominance in both cohorts. The most common racial background was Non-Hispanic White, with significant populations of Hispanics and Asian or Pacific Islanders. The neoadjuvant cohort was slightly more likely to have a higher SES. The majority of patients in both cohorts had primary tumor invasion through the muscularis propria (T3). There were more patients with node negative disease in the neoadjuvant cohort (68% vs. 37%) and consequently higher percentage of patients with all levels of node positivity in the adjuvant cohort. In patients who had undergone neoadjuvant CRT, the median number of lymph nodes examined was reduced (8 vs. 11, $p < 0.0001$). There was no overall difference in RC-SS between the neoadjuvant and adjuvant cohorts (Fig. 2).

In multivariate models for RC-SS amongst all patients, increasing age and T4 tumors were significant predictors of worse outcome regardless of treatment sequence (Table 2). There was no association between sex, race/ethnicity, or SES and RC-SS. Increasing number of positive lymph nodes was associated with worse outcome regardless of sequence, although the effect is numerically stronger and present at a lower lymph node stage in those who have been treated with neoadjuvant CRT. Those with lower numbers of lymph nodes retrieved trended towards a worse outcome, although the effect was only statistically signifi-cant for those with 8 or fewer lymph nodes retrieved (Table 2).

Similar trends for worse outcomes in both cohorts were observed for increasing age and T stage amongst those patients without positive lymph nodes identified in the surgical specimen (Table 3). Improved outcomes were observed in the highest SES group receiving neoadjuvant CRT and Asian/Pacific Islanders receiving adjuvant CRT. There was no statistically significant difference in RC-SS with lower numbers of lymph nodes retrieved in node negative patients in the neoadjuvant cohort. Compared to 12 or more lymph nodes examined, those with 3–5 or 6–8 removed before adjuvant therapy had significant inferior outcomes.

Discussion

In this retrospective study of over 4700 rectal cancer patients treated with tri-modality therapy, we investigated the prognostic implications of reduced lymph node retrieval after neoadjuvant therapy. This study corroborates prior studies that show a reduced number of lymph nodes retrieved in patients who have received neoadjuvant CRT. More importantly, we found no association between the number of lymph nodes retrieved and RC-SS in node negative patients after neoadjuvant CRT. This finding highlights a key difference between rectal and colon cancer and underscores careful interpretation of the pathologic findings when combined modality therapy is undertaken.

Although colon and rectal cancer have many biologic similarities, their treatment paradigms have diverged due to anatomic considerations. During the period of observation in this study, the proportion of patients with nonmetastatic rectal cancer receiving CRT before surgery increased. This corresponds temporally with the 2004 publication of the German Rectal Cancer Study Group trial, which showed improved local control and reduced toxicity with neoadjuvant treatment.[4] As observed in the clinical trial, there was no difference in survival outcomes based on the treatment sequence in this population-based study.

The AJCC, CAP and other groups currently recommend that a minimum of twelve lymph nodes be examined at the time of colorectal cancer resection.[7–10] The data driving this cutoff is based primarily on colon cancer studies, where the available data strongly support this recommendation.[5,6] In this study, we did observe this expected association between reduced lymph node retrieval and survival in the neoadjuvant CRT cohort. However, a statistically significant effect could only be observed with 8 or fewer lymph nodes retrieved. Moreover, similar findings were observed in the adjuvant cohort. However, the association could not be confirmed amongst patients treated with neoadjuvant therapy who did not have pathologically involved lymph nodes in their surgical specimens despite relatively robust cohort sizes to detect such an effect. This suggests that the prognostic information gained by additional lymph node assessment in those patients treated with neoadjuvant therapy is concentrated in those with node positive disease and a higher risk of recurrence.

Several studies – including this one – have demonstrated that the total number of lymph nodes retrieved at the time of primary resection is reduced after neoadjuvant CRT.[12–15] The major finding of this study is the failure to demonstrate that reduced lymph node retrieval is associated with worse outcome in node negative rectal cancer treated with neoadjuvant therapy. We did not find a threshold lymph node number below which there was an association with survival. This corroborates the findings of 2 much smaller institutional series and suggests that failure to retrieve 12 lymph nodes in this patient population is not associated with inferior outcome.[17,20] We suggest that limited lymphadenectomy should not be used to assign a separate prognosis in node negative patients when neoadjuvant trimodality treatment is planned. This study provides some support to the argument that nodal assessment should not be used as a quality care endpoint for rectal cancer patients who have undergone CRT.[21–23]

Another important observation from this study relates to the implications of residual node positivity in patients who underwent neoadjuvant CRT. In this study, more pathologic node-negative cancers were observed in the neoadjuvant cohort compared to the adjuvant cohort. This is the expected result of the eradication of positive lymph nodes by neoadjuvant CRT. However, patients with node positive disease in the neoadjuvant cohort had a numerically worse prognosis compared to those in the adjuvant cohort. This result is consistent with multiple other studies and most likely relates to more resistant tumor biology, where the persistence of cancer within a lymph node after CRT portends a greater likelihood of recurrence.[24,25] Future studies should investigate intensification of therapy or novel strategies in this subset of patients with a particularly poor prognosis.

There are several limitations to this study. As in all retrospective cohort studies, the results may have been affected by unmeasured confounding variables. Importantly, in this study we were not able to account for variability in skill among surgeons or pathologists, a factor that may impact lymph node retrieval. Pathologic assessment was performed locally and reported to the registry; therefore, we were unable to standardize the assessment. Additionally, the details of radiation and chemotherapy administration are not supplied to the registry, limiting our ability to account for variation in how treatment was administered amongst the groups. Recurrence information is not captured by the registry and we are unable to calculate recurrence free survival. Furthermore, the California Cancer Registry suffers from the same difficulties associated with other large cancer registries, including incomplete or inaccurate cancer reporting. Race and ethnicity data are particularly susceptible to misclassification bias. Nonetheless, this study assesses a large patient registry with excellent reporting standards.

In conclusion, we observed similar survival outcomes for patients treated with CRT preoperatively compared to those treated with CRT postoperatively in this large population-based study. The use of neoadjuvant CRT is increasing in frequency in California, and the implications of this transition include a lower rate of lymph node retrieval after surgery and a poor prognosis for those with residual positive lymph nodes after neoadjuvant therapy. Finally, we did not find an association between reduced lymph node number and survival in node negative patients treated with neoadjuvant CRT, suggesting that this measure does not provide useful information to inform therapeutic decision-making in this group of patients with rectal cancer.

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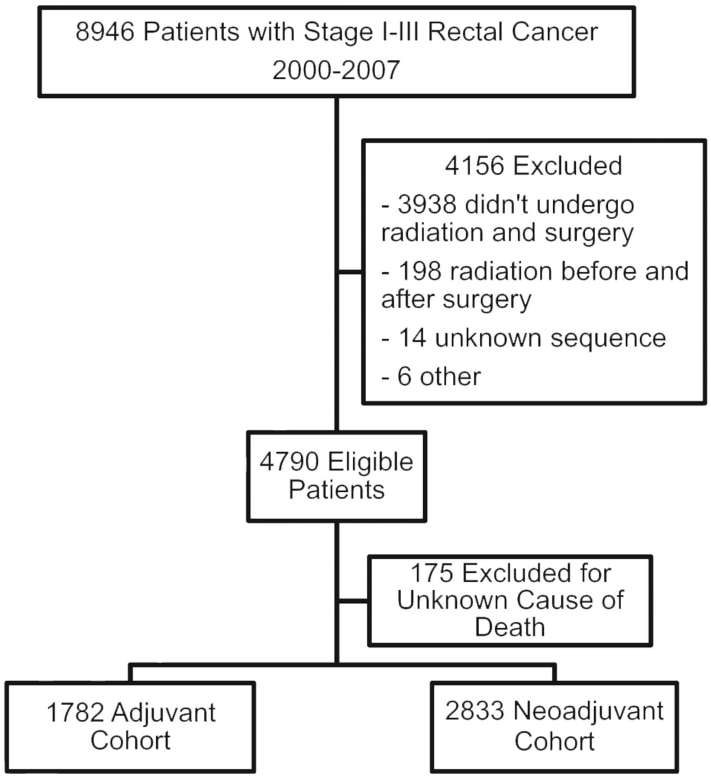

Figure 1.
Selection of rectal cancer patients included in this study.

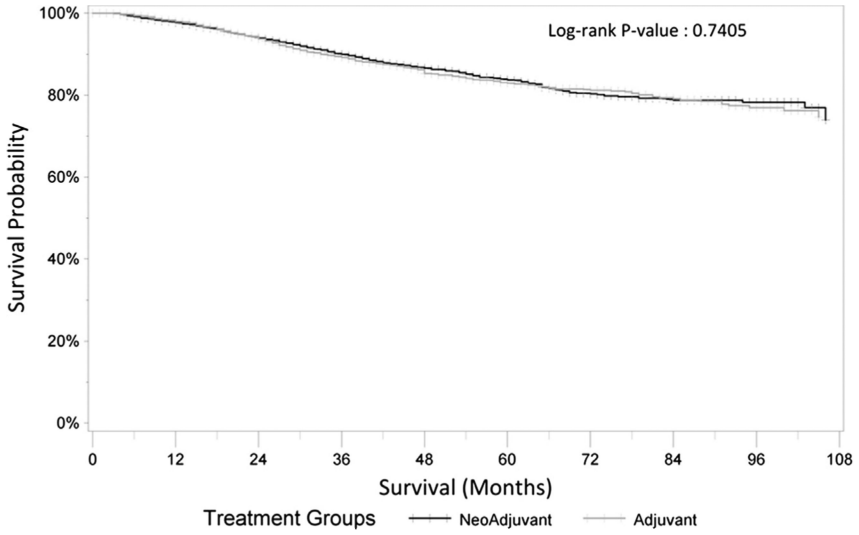

Figure 2.

Kaplan–Meier curves for rectal cancer specific survival amongst neoadjuvant and adjuvant cohorts.

Table 1

Clinical and demographic characteristics of stage I – III rectal cancer patients treated with tri-modality therapy in California 2000–2007.

Characteristic		Neoadjuvant cohort N = 2833		Adjuvant cohort N = 1782		p Value
Age (median)		59		62		<0.0001
Sex:	Male	1782	62.9%	1061	59.5%	0.0222
	Female	1051	37.1%	721	40.5%	
Race/Ethnicity:	Non-Hispanic White	1776	62.7%	1077	60.4%	0.3416
	Non-Hispanic Black	140	4.9%	93	5.2%	
	Hispanic	483	17.0%	343	19.2%	
	Asian/Pacific Islander	419	14.8%	257	14.4%	
	Other/Unknown	15	0.5%	12	0.7%	
Socioeconomic status:	1st 2nd Quintiles	884	31.2%	616	34.6%	0.0343
	3rd Quintile	585	20.6%	371	20.8%	
	4th – 5th Quintiles	1364	48.1%	795	44.6%	
T stage:	0–1	268	9.5%	99	5.6%	<0.0001
	2	512	18.1%	300	16.8%	
	3	1760	62.1%	1230	69.0%	
	4	290	10.2%	153	8.6%	
	Unknown	3	0.1%	0	0.0%	
N stage:	N0	1916	67.6%	658	36.9%	<0.0001
	N1a	341	12.0%	314	17.6%	
	N1b	292	10.3%	364	20.4%	
	N2a	146	5.2%	231	13.0%	
	N2b	138	4.9%	215	12.1%	
Nodes examined:	0–2	283	10.0%	106	5.9%	<0.0001
	3–5	569	20.1%	226	12.7%	
	6–8	571	20.2%	305	17.1%	
	9–11	469	16.6%	300	16.8%	
	12+	941	33.2%	845	47.4%	

Table 2

Multivariable Cox regression for rectal cancer specific survival amongst all patients with stage I – III rectal cancer treated with tri-modality therapy in California 2000–2007.

Characteristic		Neoadjuvant cohort N = 2833		Adjuvant cohort N = 1782	
		HR (95% CI)	p Value	HR (95% CI)	p Value
Age (continuous – 10 year increment):		1.14 (1.05–1.24)	0.0028	1.18 (1.07–1.32)	0.0016
Sex:	Male	1.00 (reference)		1.00 (reference)	
	Female	1.01 (0.81–1.25)	0.9598	0.91 (0.71–1.16)	0.4353
Race/Ethnicity:	Non-Hispanic White	1.00 (reference)		1.00 (reference)	
	Non-Hispanic Black	1.34 (0.86–2.10)	0.1984	0.96 (0.54–1.69)	0.8764
	Hispanic	1.02 (0.76–1.37)	0.8733	1.04 (0.74–1.46)	0.8137
	Asian/Pacific Islander	0.82 (0.59–1.14)	0.2431	0.93 (0.64–1.36)	0.7189
Socioeconomic status:	1st – 2nd Quintile	1.00 (reference)		1.00 (reference)	
	3rd Quintile	0.97 (0.73–1.30)	0.8400	1.32 (0.95–1.85)	0.0986
	4th – 5th Quintile	0.86 (0.67–1.12)	0.2603	1.07 (0.79–1.44)	0.6684
T stage:	0–1	1.00 (reference)		1.00 (reference)	
	2	0.86 (0.50–1.48)	0.5789	1.89 (0.66–5.42)	0.2350
	3	1.53 (0.96–2.44)	0.0745	3.74 (1.38–10.17)	0.0097
	4	3.10 (1.87–5.14)	<0.0001	5.46 (1.92–15.59)	0.0015
N stage:	N0	1.00 (reference)		1.00 (reference)	
	N1a	1.89 (1.36–2.61)	0.0001	1.14 (0.75–1.73)	0.5266
	N1b	2.18 (1.57–3.03)	<0.0001	1.54 (1.07–2.22)	0.0210
	N2a	3.75 (2.61–5.40)	<0.0001	2.60 (1.76–3.83)	<0.0001
	N2b	6.37 (4.40–9.23)	<0.0001	5.43 (3.71–7.93)	<0.0001
Nodes examined:	0–2	1.67 (1.10–2.54)	0.0168	1.74 (1.10–2.54)	0.0680
	3–5	1.77 (1.28–2.46)	0.0006	2.19 (1.48–3.23)	<0.0001
	6–8	1.68 (1.23–2.29)	0.0111	1.79 (1.26–2.53)	0.0010
	9–11	1.35 (0.97–1.88)	0.0747	1.30 (0.92–1.85)	0.1401
	12+	1.00 (reference)		1.00 (reference)	

Table 3

Multivariable Cox regression for rectal cancer specific survival amongst pathologic node-negative patients treated with tri-modality therapy in California 2000–2007.

Characteristic		Neoadjuvant cohort N = 1916		Adjuvant cohort N = 658	
		HR (95% CI)	p value	HR (95% CI)	p Value
Age (continuous – 10 year increment):		1.14 (1.00–1.29)	0.0468	1.22 (0.92–1.51)	0.0748
Sex:	Male	1.00 (reference)		1.00 (reference)	
	Female	1.08 (0.79–1.49)	0.6288	1.02 (0.62–1.68)	0.4353
Race/Ethnicity:	Non-Hispanic White	1.00 (reference)		1.00 (reference)	
	Non-Hispanic Black	1.39 (0.72–2.69)	0.3274	0.43 (0.10–1.80)	0.2467
	Hispanic	1.03 (0.66–1.59)	0.9074	0.78 (0.39–1.57)	0.4873
	Asian/Pacific Islander	0.96 (0.61–1.52)	0.8695	0.33 (0.12–0.93)	0.0364
Socioeconomic status:	1st – 2nd Quintile	1.00 (reference)		1.00 (reference)	
	3rd Quintile	0.83 (0.55–1.26)	0.3776	2.04 (1.09–3.82)	0.0253
	4th – 5th Quintile	0.69 (0.47–1.00)	0.0498	1.14 (00.61–2.12)	0.6909
T stage:	0–1	1.00 (reference)		1.00 (reference)	
	2	1.27 (0.65–2.45)	0.4835	2.03 (0.44–9.45)	0.3681
	3	1.76 (0.98–3.16)	0.0594	2.20 (0.53–9.19)	0.2806
	4	4.64 (2.47–8.74)	<0.0001	4.18 (0.90–19.34)	0.0672
Nodes examined:	0–2	1.38 (0.84–2.27)	0.2074	1.67 (0.67–4.20)	0.2723
	3–5	1.38 (0.88–2.17)	0.1638	3.02 (1.49–6.13)	0.0021
	6–8	1.20 (0.74–1.93)	0.4552	2.18 (1.08–4.40)	0.0301
	9–11	1.10 (0.64–1.87)	0.7390	1.84 (0.84–4.02)	0.1274
	12+	1.00 (reference)		1.00 (reference)	