Published in final edited form as:

J Surg Oncol. 2013 June ; 107(8): . doi:10.1002/jso.23332.

Adequate Lymph Node Recovery Improves Survival in Colorectal Cancer Patients

ADEDAYO A. ONITILO, MD, MSCR, FACP^{1,2,3,4}, RACHEL V. STANKOWSKI, PHD², JESSICA M. ENGEL, MS, RN³, and SUHAIL A. R. DOI, FRCP, PHD⁴

¹Department of Hematology and Oncology, Marshfield Clinic, Weston Center, Weston, Wisconsin

²Marshfield Clinic Research Foundation, Marshfield, Wisconsin

³Department of Hematology and Oncology, Marshfield Clinic Cancer Care at St Michaels Stevens Point, Wisconsin

⁴Clinical Epidemiology Unit, School of Population Health, University of Queensland, Brisbane, Australia

Abstract

Introduction—Current recommendations suggest recovery of 12 lymph nodes during surgical resection for colorectal cancer (CRC) for proper staging and prognostication. Adequate lymph node recovery has been associated with improved patient survival, with results inconsistent.

Methods—We examined factors for association with adequate lymph node recovery and used findings to adjust survival analyses to clarify whether adequate lymph node examination is associated with CRC survival or associated with a subset of characteristics that biases lymph node recovery.

Results—In 74% of subjects (1036/1397) adequate number of lymph nodes were examined. A stepwise multivariate regression analysis showed procedure year, cancer stage, tumor size, and age at diagnosis were significantly associated with lymph node recovery. These and other factors associated with survival status were adjusted for in further analyses, revealing no difference in unadjusted overall survival by adequacy of lymph node recovery (HR=0.90, 95% CI 0.75–1.08, $P=0.239$). However, in adjusted Cox proportional hazards analysis, adequate lymph node recovery was associated with reduced risk for death (HR=0.71, 95% CI 0.57–0.89, $P=0.002$).

Conclusion—The current recommendation for retrieval and examination of at least 12 lymph nodes is appropriate for proper treatment and prognostication in patients undergoing surgical resection for CRC.

Keywords

colorectal cancer; lymph node recovery; survival; staging

INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of new cancer cases and death among men and women in the United States. The American Cancer Society estimates that in 2011, there will be 141,210 new cases and 49,380 deaths from CRC [1]. Throughout the last

Correspondence to: Adedayo A. Onitilo, Department of Hematology/Oncology, Marshfield Clinic Weston Center, 3501 Cranberry Boulevard, Weston, WI 54476 USA. Tel. 715-393-1400. Fax. 715-393-1399. onitilo.adedayo@marshfieldclinic.org.

Conflict of interest statement: All authors state that they have no real or potential conflicts of interest.

decade mortality rates from CRC have continued to decline due to enhanced prevention, screening for earlier detection, diagnosis with better preoperative staging, enhanced techniques for surgical treatment, and improved pathologic staging to inform adjuvant treatment decisions and prognosis [2,3].

En-bloc surgical resection with draining mesenteric lymph nodes is curative for early stage (I–II) CRC [4]. Cases with positive nodes (stage III) receive chemotherapy as standard adjuvant treatment, reducing disease-specific mortality by 30% [4,5]. However, up to 30% of patients with stage I–II CRC die of disease recurrence or metastasis and may likely have had extra-colonic disease that remained undetected during diagnosis and surgery [6]. Suboptimal surgical lymph node harvesting can result in understaging of the patient and cause potentially life-saving adjuvant therapy to be withheld. Conversely, if a patient rightly staged at stage II is provided with chemotherapy due to fear of understaging, the patient may be exposed unnecessarily to 6 months of chemotherapy with lifelong effects on quality of life. Extensive lymphadenectomy is thought to improve accuracy in staging and may also enhance the curative effect of surgery by removing metastatic lymph nodes.

Many studies have demonstrated that insufficient lymph node examination is associated with shorter overall survival in both node-negative and node-positive CRC patients [7–13]. The National Comprehensive Cancer Network, American Joint Committee on Cancer, and American College of Pathologists recommend the examination of at least 12 lymph nodes for adequate CRC staging [3,14,15]. Still, other studies have found no association between lymph node recovery and survival in CRC patients [16–21]. When examining the relationship between lymph node recovery and survival in CRC patients, investigators frequently adjust for factors known to affect CRC survival, including certain patient demographic and tumor characteristics [10,21]. Several factors have also been associated with adequate lymph node recovery during surgical resection and specimen examination. Therefore, groups of patients classified by adequate or inadequate lymph node examination will have bias based on one or another of these factors. We hypothesized that adjustment of survival analyses for specific covariates found to influence lymph node recovery and survival may help to clarify whether adequate lymph node examination is truly associated with CRC survival, or if it is associated with another subset of patient characteristics that biased lymph node recovery. In the present study, a large number of patient, disease, and provider characteristics were examined for association with adequate lymph node recovery and survival and the findings were used to adjust survival analyses.

METHODS

This was a retrospective study of a patient population consisting of histologically confirmed primary stage I–III CRC cases occurring at the Marshfield Clinic from January 1, 1992 to December 31, 2008. Study approval was granted by the Marshfield Clinic's institutional review board. Demographic and clinical characteristics, cancer surgery details, other treatment information, and other follow-up data were extracted from the Marshfield Virtual Data Warehouse, Marshfield Clinic/St. Joseph's Hospital Cancer Registry, and the Marshfield Clinic electronic medical record (EMR) system. Other relevant data were collected largely through abstraction of the EMR. Manual chart review was performed to validate electronic data. Specific information regarding the surgeon/pathologist not available through the Marshfield Clinic Virtual Data Warehouse was obtained from Marshfield Clinic employee information/human resources. The number of lymph nodes examined was obtained from a defined field in the cancer registry data. Adequate nodal evaluation was defined as 12 or more lymph nodes examined.

Baseline subject characteristics were first compared according to adequacy of lymph node recovery. Chi-square tests or, where cell frequencies were small, Fisher's exact tests were used to compare categorical variables between the groups. The Wilcoxon rank sum test was used to compare continuous outcomes between the two groups. Multivariate logistic regression was used to examine associations between adequacy of lymph node recovery (dichotomous) and covariates of interest. Survival distributions for lymph node recovery adequacy groups and other subject characteristics were estimated using the Kaplan-Meier method and the comparability of the distribution was tested using the log-rank test. Cox proportional hazards regression was used to model the survival data on lymph node recovery adequacy while adjusting for other covariates and testing for interactions among them. The primary end point of the study in terms of survival analysis was overall survival. All models were fitted via stepwise forward selection and reported *P*-values are two-sided and were compared with a 0.05 significance level. All analyses were performed using SPSS version 20.

RESULTS

There were 1437 CRC cases identified for analysis from January 1, 1992 to December 31, 2008. Exclusion of 40 patients with an undocumented number of lymph nodes resulted in 1397 cases for analysis. Median follow-up time was 63 months. Adequate lymph node recovery was defined as recovery of 12 or more lymph nodes at the time of surgical resection. Lymph node recovery was adequate in 1036 (74.2%) patients and inadequate in 361 (25.8%) patients. As expected, the mean number of lymph nodes examined and number of positive lymph nodes was significantly higher in patients with adequate lymph node recovery ($P < 0.0001$) (Table 1). The lymph node ratio, defined as the number of positive lymph nodes divided by the total number of lymph nodes recovered, was significantly greater in patients with inadequate lymph node recovery ($P = 0.0082$) (Table 1).

We examined an extensive list of variables for association with adequate lymph node recovery. Factors examined included patient demographic, clinical characteristics, disease characteristics, surgical characteristics, and surgeon characteristics. In the interest of space, clinical characteristics including comorbid myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular disease, dementia, chronic pulmonary disease, peptic ulcer disease, rheumatologic disease, mild liver disease, moderate or severe liver disease, diabetes, chronic complications of diabetes, hemiplegia, renal disease, secondary malignancy, acquired immune deficiency syndrome, and other surgery were excluded from the tables. The Charlson score, which takes comorbid conditions into account, is included. None of the aforementioned clinical characteristics were associated with adequate lymph node recovery. Univariate associations between the remaining characteristics with adequate lymph node recovery are shown in Table 2. Factors significantly associated with adequate lymph node recovery included higher cancer stage, higher cancer grade, higher pathological N and T, larger tumor size, node positive status, greater negative margin distance, and procedure year (Table 2). Variables found to be significantly associated with lymph node recovery were used to perform a stepwise multivariate logistic regression analysis. Age was also included in the model due to known clinical significance. Despite association with lymph node recovery in the univariate analysis, pathological N and T and node positive status were not included in the multivariate analysis due to tight correlations with stage and tumor size. Variables with greater than 20% missing data were also excluded from the multivariate analysis. Variables significantly associated with adequate lymph node recovery and included in the final model were procedure year, cancer stage, and tumor size, in addition to the forced addition of age (Table 3).

Many more factors were associated with survival by Kaplan Meier analysis (Table 4). Covariates for adjustment of the final survival analyses included variables significantly associated with adequate lymph node recovery and those significantly associated with survival (Table 4). Disease recurrence occurred in only 20 (1.4%) patients, leaving insufficient power for examination of disease-specific survival. Median survival time was 118 months. Patients with adequate lymph node recovery survived a median of 120 months post-surgery, while patients with inadequate lymph node recovery survived a median of 105 month post-surgery. The difference was not significant ($P = 0.111$).

Notably, adjuvant chemotherapy use, which is generally dictated by post-surgical staging, was greater in patients with adequate lymph node recovery (391/1036; 37.7%) compared to those with inadequate lymph node recovery (100/361; 27.7%) ($P = 0.001$). Use of adjuvant chemotherapy was also significantly associated with survival (Table 4). Subjects who received adjuvant chemotherapy survived for a median of 144 months compared to 107 months for those who did not receive adjuvant chemotherapy ($P = 0.001$). Therefore, we chose to adjust for adjuvant chemotherapy use in our Cox proportional hazards model. There was no difference in unadjusted overall survival between patients with and without adequate lymph node recovery (Table 5). However, in a Cox proportional hazards analysis adjusted for cancer stage, margin status, use of adjuvant chemotherapy, age at diagnosis, and Charlson score adequate lymph node recovery was associated with a reduced risk for death (hazard ratio [HR] = 0.71; 95% confidence interval [CI] 0.57–0.88, $P = 0.002$) (Table 5).

When the effect of adjuvant chemotherapy administration was assessed separately for those with and without adequate lymph node recovery, we found that survival increased significantly with chemotherapy use for both stage II and III CRC in both groups (Table VI). Survival time was greater for subjects with adequate lymph node recovery regardless of whether or not chemotherapy was administered, especially for stage III CRC, where survival time with chemotherapy was 92.7 months with inadequate and 121.1 months with adequate lymph node recovery and 49.3 months vs. 76.4 months, respectively, without chemotherapy.

Some investigators suggest that the lymph node ratio (LNR), or the ratio of positive lymph nodes to the total number of lymph nodes examined, is a better prognostic indicator than lymph node recovery. To examine the effects of LNR and adequate lymph node recovery on survival, we grouped patients into four groups based on whether their LNR indicated node negative (LNR = 0) or node positive (LNR > 0) CRC and whether or not lymph node recovery was adequate. Survival was significantly different for all four groups (Figure 1) with greatest survival in subjects with node negative CRC and adequate lymph node recovery and poorest survival in subjects with node positive CRC and inadequate lymph node recovery (Table VII).

DISCUSSION

Adequate lymph node recovery is important for proper staging of CRC and has been shown to be associated with patient survival. In the present study, a high percentage of subjects (74%) had an adequate number of lymph nodes (≥ 12) examined. This is consistent with the findings in a recent multicenter study by Kanemitsu et al [12], in which 50%–81.8% of patients had adequate lymph node recovery using the same definition. We examined an extensive list of patient and provider characteristics for association with lymph node recovery, identified several predictive variables, and confirmed the utility of 12 lymph nodes as a meaningful goal for adequate lymph node recovery that predicts improved survival.

Several patient, disease, and provider characteristics have been associated with adequate lymph node recovery. A recent review of the literature by Storli et al [22] found that many

factors have been associated with lymph node harvest including patient gender and age, hospital volume, surgeon volume and competence/qualifications, specimen characteristics including length, tumor location, differentiation and mucinous histology, T stage, reactive changes or inflammation, and pathology technique including the qualifications, competence or dedication of the pathologist, specimen preparation, length of fixation, lymph node preservation fluid, and fat solvent. Other more recent studies found age, tumor stage, location and size [12,23]; tumor diameter [24]; age, gender, tumor stage, grade, and N stage [10]; procedure year [25]; and pathologist years in training [26] to be associated with adequate lymph node retrieval during surgical resection for CRC. In the present study, factors found to be associated with adequate lymph node examination included cancer stage, cancer grade, tumor size, pathological T and N stages, procedure year, and positive node status. All of these factors have been identified previously and are consistent with the literature [12,22,25]. In a stepwise multivariate regression analysis, procedure year, cancer stage, tumor size, and age at diagnosis (which was forced into the model) were identified as the factors most significantly associated with lymph node recovery. Procedure year may have influenced how the surgical resection procedure was performed, affecting lymph node recovery. Cancer stage and tumor size may reflect disease severity, and those with more advanced stage and larger tumors may be more likely to undergo extensive surgical resection, improving lymph node recovery. Age was forced into the multivariate models due to clinical importance, and its significance is consistent with previous studies [22].

Many studies have demonstrated that insufficient lymph node examination is associated with shorter overall survival in both node-negative and node-positive CRC patients [7–13]. In 2007, Chang and colleagues [27] published a comprehensive systematic review of 17 studies that examined lymph node recovery as it relates to CRC survival. Although the threshold for lymph nodes considered adequate varied widely amongst studies, most found a survival benefit associated with examination of more lymph nodes. A positive correlation between lymph node recovery and survival was observed in 16/17 studies of stage II CRC and 4/6 studies of stage III CRC [27]. Our findings are in agreement with the majority of studies suggesting that increased lymph node recovery is associated with survival.

Although it is generally accepted that recovering more lymph nodes results in increased survival, there is some disagreement regarding how many lymph nodes should be recovered to be considered adequate. In the studies reviewed by Chang et al [27], the number of lymph nodes recommended ranged from 6 to 40. The National Comprehensive Cancer Network, American Joint Committee on Cancer, and American College of Pathologists recommend the examination of at least 12 lymph nodes for adequate CRC staging [3,14,15]. Until relatively recently, however, scientific evidence in support of the use of 12 lymph nodes as a threshold was sparse. A recent study by Kanemitsu and colleagues [12] examined over 4500 patients at several centers in Japan and found that patients with stage II or III CRC that had 12 or more lymph nodes examined had better survival than those with fewer than 12 lymph nodes examined, supporting a 12-node threshold. Choi et al [8] and Chen et al [10] also observed increased survival for subjects with 12 or more lymph nodes examined. Furthermore, in a 2010 study by Fan and colleagues [28], when additional searches were performed to increase the number of CRC cases with 12 nodes, positive nodes were found in a significant number of cases resulting in tumor upstaging in almost 15% of the cases in which an additional search for nodes was performed [28]. Still, other studies have found no association between lymph node recovery and survival in CRC patients [16–21]. Our findings support the use of a threshold of 12 lymph nodes in determining adequacy of lymph node recovery during surgical resection for CRC. We observed a significant survival advantage in patients who had more than 12 lymph nodes recovered. The exact “best” threshold is likely to vary somewhat between patient populations, but the recommendation for recovery of 12 lymph nodes is likely to provide a good guideline for adequate recovery.

The exact mechanism by which adequate lymph node recovery affects survival is unclear and is likely to be multifactorial. Popular theories include proper staging and the therapeutic benefit of removing nodes with potential micrometastases. In the present study, we noted that adjuvant chemotherapy was more frequently administered to patients with adequate than inadequate lymph node recovery. Use of adjuvant chemotherapy was also associated with survival. Adjuvant chemotherapy is administered after pathological analysis as a result of lymph node metastasis. Adjuvant chemotherapy is routinely provided to patients with stage III CRC, but its use in patients with stage II CRC is controversial, as it results in only small improvement compared to observation alone [29]. The decreased use of adjuvant chemotherapy in patients with inadequate lymph node recovery may be caused by an increased likelihood of understaging in these patients and may have an impact on survival. Patients understaged as a result of inadequate lymph node recovery run the risk of having potentially life-saving adjuvant chemotherapy withheld. Conversely, if a patient is staged correctly at stage II despite inadequate lymph node recovery and adjuvant chemotherapy is administered due to fear of understaging, the patient may be unnecessarily exposed to chemotherapy with long-term effects on quality of life. The data presented here support the notion that adjuvant chemotherapy should be administered empirically to patients with fewer than 12 lymph nodes recovered. For patients with stage II or III CRC and inadequate lymph node recovery, survival time was significantly greater in those who received adjuvant chemotherapy than in those who did not. Interestingly, this was also true in patients with stage II and III CRC who had adequate lymph node recovery. Of note, survival time was greater for subjects with adequate lymph node recovery, regardless of whether or not chemotherapy was administered, especially for stage III CRC.

The recommendation for examination of 12 lymph nodes during surgical resection for CRC was made as early as 1989 [30]. However, in the United States, from 1988 to 2000 the median number of lymph nodes examined was only nine [7], and only 37% of CRC resection cases reported recovery of at least 12 lymph nodes [31]. Some improvement in recovery of at least 12 lymph nodes may have occurred in recent years. Seventy-four percent of subjects in our study had 12 or more lymph nodes recovered, and in the multicenter study published recently by Kanemitsu et al [12], 50%–82% of subjects at the different institutions in Japan had adequate lymph node recovery by the same definition. In conjunction with the reports by Choi et al [8], Chen et al [10], Kanemitsu et al [12], and Fan et al [28], our findings support the use of 12 lymph nodes as a threshold for adequate recovery to prevent understaging and increase overall survival following surgical resection for CRC. Some suggest that lymph node ratio (ratio of positive to total lymph nodes) may be a better prognostic indicator for CRC than number of lymph nodes recovered [9]. However, even lymph node ratio has been found to provide a more accurate prognosis when a minimum of 12 lymph nodes have been collected [10]. In the present study, subjects with fewer than 12 lymph nodes recovered had a higher mean lymph node ratio than those with more than 12 nodes, even though a greater number of positive nodes was found in those with adequate recovery. We believe this difference is related to the denominator of total lymph nodes recovered. Importantly, in the surgical and pathological settings, retrieval of at least 12 lymph nodes is more feasible than a cut-off lymph node ratio, although lymph node ratio may still have an important role in prognosis. In our analysis of the combined effects of lymph node ratio and lymph node recovery, we found the two factors to independently affect survival with the greatest survival in those with a lymph node ratio indicating node negative cancer and adequate lymph node recovery, suggesting that administration of adjuvant chemotherapy to node negative subjects with inadequate lymph node recovery may improve survival.

The retrospective nature of the present study limits our ability to account for all potential bias or confounders statistically. Additionally, we did not perform separate analysis for

colon and rectal cancer in the present study. We found many factors that were associated with both lymph node recovery and survival, suggesting that the relationship is quite complex. The present study was also limited by sample size and missing data. For example, clinical T appeared to be significantly associated with adequate lymph node recovery, but missing data prohibited its use in the stepwise multivariate regression analysis. Differential use of adjuvant chemotherapy in subjects with and without adequate lymph node recovery may also be a confounding factor. We adjusted for chemotherapy use in our Cox proportional hazards model, but future studies addressing the role adjuvant chemotherapy plays in the relationship between lymph node recovery and survival may be warranted. Finally, the small number of patients with recurrent CRC did not allow for analysis of disease-free survival.

CONCLUSION

Assessment of lymph nodes for metastases is an important part of CRC diagnosis and treatment. Therefore, retrieval of an adequate number of lymph nodes is essential to making informed clinical decisions for management after surgical resection for CRC. We demonstrated that lymph node recovery is affected by several patient and provider characteristics, and that adequate recovery of at least 12 lymph nodes can improve overall survival. In conjunction with reports from other sites, we conclude that the recommendation for retrieval of at least 12 lymph nodes is appropriate for proper staging and treatment decisions. Adjuvant chemotherapy may help to improve survival in node negative CRC patients with inadequate lymph node recovery. Further studies examining the relationship between lymph node recovery, adjuvant chemotherapy administration, and survival are warranted.

Acknowledgments

Study support was provided by NIH Grant Number U19 CA 79689 entitled “Cancer Research Network Across Health Care Systems.”

The authors thank Dr. Po-Huang Chyou of the Marshfield Clinic Research Foundation’s Biomedical Informatics Research Center for providing statistical assistance. The authors also thank Marie Fleisner of the Marshfield Clinic Research Foundation’s Office of Scientific Writing and Publication for editorial assistance in the preparation of this manuscript.

References

1. American Cancer Society. [Accessed June 2, 2011] Learn About Cancer: Colorectal Cancer Overview. Available at: <http://www.cancer.org/Cancer/ColonandRectumCancer/OverviewGuide/colorectal-cancer-overview-key-statistics>
2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. *CA Cancer J Clin.* 2007; 57:43–66. [PubMed: 17237035]
3. Washington MK. Colorectal carcinoma: selected issues in pathologic examination and staging and determination of prognostic factors. *Arch Pathol Lab Med.* 2008; 132:1600–1607. [PubMed: 18834218]
4. Lee HY, Choi HJ, Park KJ, et al. Prognostic significance of metastatic lymph node ratio in node-positive colon carcinoma. *Ann Surg Oncol.* 2007; 14:1712–1717. [PubMed: 17253102]
5. Gray R, Barnwell J, et al. Quasar Collaborative Group. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet.* 2007; 370:2020–2029. [PubMed: 18083404]
6. Feezor RJ, Copeland EM 3rd, Hochwald SN. Significance of micrometastases in colorectal cancer. *Ann Surg Oncol.* 2002; 9:944–953. [PubMed: 12464585]
7. Chen SL, Bilchik AJ. More extensive nodal dissection improves survival for stages I to III of colon cancer. *Ann Surg.* 2006; 244:602–610. [PubMed: 16998369]

8. Choi HK, Law WL, Poon JT. The optimal number of lymph nodes examined in stage II colorectal cancer and its impact on outcomes. *BMC Cancer*. 2010; 10:267–276. [PubMed: 20529352]
9. Noura S, Ohue M, Kano S, et al. Impact of metastatic lymph node ratio on node-positive colorectal cancer. *World J Gastrointest Surg*. 2010; 2:70–77. [PubMed: 21160853]
10. Chen SL, Steele SR, Eberhardt J, et al. Lymph node ratio as a quality and prognostic indicator in stage III colon cancer. *Ann Surg*. 2011; 253:82–87. [PubMed: 21135690]
11. Ishizuka M, Nagata H, Takagi K, et al. Insufficient lymph node dissection is an independent risk factor for postoperative cancer death in patients undergoing surgery for stage II colorectal cancer. *Eur Surg Res*. 2011; 46:57–64. [PubMed: 21135561]
12. Kanemitsu Y, Komori K, Ishiguro S, et al. The relationship of lymph node evaluation and colorectal cancer survival after curative resection: a multi-institutional study. *Ann Surg Oncol*. 2012; 9:2169–2177. [PubMed: 22302263]
13. Kotake K, Honjo S, Sugihara K, et al. Number of lymph nodes retrieved is an important determinant of survival of patients with stage II and III colorectal cancer. *Jpn J Clin Oncol*. 2012; 4:29–35. [PubMed: 22102737]
14. Compton CC, Fielding LP, Burgart LJ, et al. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. *Arch Pathol Lab Med*. 2000; 124:979–994. [PubMed: 10888773]
15. National Comprehensive Cancer Network (NCCN). [Accessed June 2, 2011] NCCN Clinical Practice Guidelines in Oncology: Colon Cancer, Version 3.2011. Available at: http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf
16. Schumacher P, Dineen S, Barnett C Jr, et al. The metastatic lymph node ratio predicts survival in colon cancer. *Am J Surg*. 2007; 194:827–832. [PubMed: 18005779]
17. Derwinger K, Carlsson G, Gustavsson B. A study of lymph node ratio as a prognostic marker in colon cancer. *Eur J Surg Oncol*. 2008; 34:771–775. [PubMed: 18079086]
18. Peng J, Xu Y, Guan Z, et al. Prognostic significance of the metastatic lymph node ratio in node-positive rectal cancer. *Ann Surg Oncol*. 2008; 15:3118–3123. [PubMed: 18769971]
19. Kim YS, Kim JH, Yoon SM, et al. Lymph node ratio as a prognostic factor in patients with stage III rectal cancer treated with total mesorectal excision followed by chemoradiotherapy. *Int J Radiat Oncol Biol Phys*. 2009; 74:796–802. [PubMed: 19289261]
20. Moug SJ, Saldanha JD, McGregor JR, et al. Positive lymph node retrieval ratio optimizes patient staging in colorectal cancer. *Br J Cancer*. 2009; 100:1530–1533. [PubMed: 19401684]
21. Vaccaro CA, Im V, Rossi GL, et al. Lymph node ratio as prognosis factor for colon cancer treated by colorectal surgeons. *Dis Colon Rectum*. 2009; 52:1244–1250. [PubMed: 19571700]
22. Storli K, Lindboe CF, Kristofferson C, et al. Lymph node harvest in colon cancer specimens depends on tumour factors, patients and doctors, but foremost on specimen handling. *APMIS*. 2010; 119:127–134. [PubMed: 21208280]
23. Lagoudianakis E, Pappas A, Koronakis N, et al. Lymph node harvesting in colorectal carcinoma specimens. *Tumori*. 2011; 97:74–78. [PubMed: 21528668]
24. Minhas JS, Igali L. Lymph node correlations and thresholds in colorectal cancer specimens. *Int J Surg Pathol*. 2011; 19:462–468. [PubMed: 21427101]
25. Porter GA, Urquhart R, Bu J, et al. Improving nodal harvest in colorectal cancer: so what? *Ann Surg Oncol*. 2012; 19:1066–1073. [PubMed: 21969083]
26. Bamboat ZM, Deperalta D, Dursun A, et al. Factors affecting lymph node yield from patients undergoing colectomy for cancer. *Int J Colorectal Dis*. 2011; 26:1163–1168. [PubMed: 21573900]
27. Chang GJ, Rodriguez-Bigas MA, Skibber JM, et al. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. *J Natl Cancer Inst*. 2007; 99:433–441. [PubMed: 17374833]
28. Fan L, Levy M, Aguilar CE, et al. Lymph node retrieval from colorectal resection specimens for adenocarcinoma: is it worth the extra effort to find at least 12 nodes? *Colorectal Dis*. 2011; 13:1377–1383. [PubMed: 20969717]
29. Zhou Z, Wu X, Wang R, et al. Optimal use of adjuvant chemotherapy in stage II colorectal cancer. *Int J Colorectal Dis*. 2011; 26:867–873. [PubMed: 21431851]

30. Scott KWM, Grace RH. Detection of lymph node metastases in colorectal carcinoma before and after fat clearance. *Br J Surg*. 1989; 78:1165–1167. [PubMed: 2688803]
31. Baxter NN, Virnig DJ, Rothenberger DA, et al. Lymph node evaluation in colorectal cancer patients: a population-based study. *J Natl Cancer Inst*. 2005; 97:219–225. [PubMed: 15687365]

Figure 1.

Table I

Number of Lymph Nodes Examined, Number of Positive Nodes, and Lymph Node Ratio in Patients with Adequate and Inadequate Lymph Node Recovery

	Adequate (≥ 12) (N = 1036)	Inadequate (< 12) (N = 361)	P-value ^a
Lymph nodes examined			
Mean (range)	23.5 (12–90)	7.3 (1–11)	<0.0001
Positive lymph nodes			
Mean (range)	1.55 (0–27)	0.67 (0–9)	<0.0001
Lymph node ratio (positive/total)			
Mean (range)	0.07 (0.00–1.00)	0.09 (0.00–1.00)	0.0082

^aWilcoxon Two-Sample Test

Table II

Association of Patient and Provider Characteristics with Adequate Lymph Node Recovery

Lymph Node Recovery			
	Adequate (≥ 12) n (%)	Inadequate (< 12) n (%)	P-value
Patient Demographic Characteristics			
Gender			0.393
Female	524 (50.6)	173 (47.9)	
Male	512 (49.4)	188 (52.1)	
Education			0.102
High School	758 (80.2)	256 (76.0)	
> High School	187 (19.8)	81 (24.2)	
Employment			0.771
Employed	261 (29.1)	87 (28.1)	
Unemployed	636 (70.9)	223 (71.9)	
Marital Status			0.198
Married	676 (65.6)	219 (61.7)	
Unmarried	355 (34.4)	136 (38.3)	
Disease Characteristics			
Cancer Stage			<0.0001
I	244 (23.5)	141 (39.1)	
II	379 (36.6)	116 (32.1)	
III	413 (39.9)	104 (28.8)	
Cancer Grade			0.020
G1 (well-differentiated)	55 (5.4)	25 (7.1)	
G2 (moderately-differentiated)	730 (71.6)	268 (76.6)	
G3 (poorly-differentiated)	235 (23.0)	57 (16.3)	
Obstruction			0.121
Yes	221 (21.9)	60 (17.9)	
No	787 (78.1)	276 (82.1)	
Perforation			0.882
Yes	47 (4.7)	16 (4.8)	
No	955 (95.3)	315 (95.2)	
Margins			0.860
Positive	33 (3.4)	10 (3.1)	
Negative	924 (96.6)	311 (96.9)	
Pathological M			0.053
0	765 (99.9)	259 (98.8)	
1	1 (0.1)	3 (1.1)	
Pathological N			<0.0001
0	622 (61.2)	258 (73.3)	
1	258 (25.4)	72 (20.5)	
2	137 (13.5)	22 (6.3)	

Lymph Node Recovery					
		Adequate (≥ 12) n (%)		Inadequate (< 12) n (%)	P-value
<hr/>					
Pathological T					<0.0001
1		127 (12.5)		81 (23.1)	
2		182 (17.9)		74 (21.1)	
3		622 (61.2)		167 (47.6)	
4		85 (8.4)		29 (8.3)	
Nodes Positive Status					<0.0001
Yes		405 (39.1)		95 (26.3)	
No		631 (60.9)		266 (73.7)	
<hr/>					
Surgery Characteristics					
Surgery					0.410
Emergency		112 (12.1)		31 (10.2)	
Elective		817 (87.9)		274 (89.8)	
Procedure Year					<0.0001
1992–1997		370 (35.7)		71 (19.7)	
1998–2003		338 (32.6)		175 (48.5)	
2004–2009		328 (31.7)		115 (31.9)	
<hr/>					
Surgeon Characteristics					
Surgeon Gender					0.294
Female		8 (0.9)		4 (1.8)	
Male		835 (99.1)		223 (98.2)	
Surgeon Volume					0.071
Low (< 75 per year)		248 (29.4)		83 (37.0)	
Medium (75–120 per year)		390 (46.3)		88 (39.3)	
High (> 120 per year)		205 (24.3)		53 (23.7)	
<hr/>					
Continuous Variables	N	Median	N	Median	P-value
Age at Diagnosis	1036	70	361	71	0.393
Charlson Score	1036	0	361	0	0.220
Tumor Size (mm)	948	43	297	35	<0.0001

Table IIIMultivariate Logistic Regression Analysis for Association with Lymph Node Recovery^a

Variables	Odds Ratio (OR)	95% CI	P-value
Procedure Year			
1992–1997	Ref		
1998–2003	0.399	0.280–0.569	<0.001
2004–2009	0.476	0.332–0.683	<0.001
Cancer Stage			
I	Ref		
II	0.399	0.280–0.569	0.028
III	0.476	0.332–0.683	0.001
Tumor Size (mm)	1.014	1.007–1.021	<0.001
Age at Diagnosis (years)	0.988	0.977–1.000	0.046

^aVariables entered into the model for forward stepwise selection ($P < 0.05$ to enter) include stage, grade, tumor size, procedure year, and diagnosis age.

Table IV**Median Survival by Patient and Provider Characteristics**

Characteristics	N (%)	Median Survival (months)	P-value (log rank)
Patient Characteristics			
Gender			0.076
Female	697 (49.9)	121	
Male	700 (50.1)	108	
Education			0.599
High School	1014 (79.1)	108	
>High School	268 (20.9)	133	
Employment			<0.001
Employed	348 (28.8)	205	
Unemployed	859 (71.2)	90	
Marital Status			<0.001
Married	895 (64.1)	145	
Unmarried	491 (35.2)	79	
Disease Characteristics			
Cancer Stage			<0.001
I	385 (27.6)	166	
II	495 (35.4)	116	
III	517 (37.0)	76	
Cancer Grade			<0.001
G1 (well-differentiated)	80 (5.8)	189	
G2 (moderately-differentiated)	998 (72.8)	115	
G3 (poorly-differentiated)	292 (21.3)	92	
Obstruction			<0.001
Yes	281 (20.2)	74	
No	1063 (76.5)	133	
Perforation			0.002
Yes	63 (4.7)	78	
No	1270 (95.3)	125	
Margins			<0.001
Positive	43 (3.4)	39	
Negative	1235 (96.6)	120	
Pathological M			0.005
0	1024 (99.6)	111	
1	4 (0.4)	6	
Pathological N			<0.001
0	880 (64.3)	140	
1	330 (24.1)	92	
2	159 (11.6)	52	
Pathological T			<0.001

Characteristics	N (%)	Median Survival (months)	P-value (log rank)
1	208 (15.2)	192	
2	256 (18.7)	136	
3	789 (57.7)	95	
4	8.3 (114)	56	
Nodes Positive Status			<0.001
Yes	897 (64.2)	140	
No	500 (35.8)	73	
Surgery Characteristics			
Surgery			<0.001
Emergency	143 (11.6)	55	
Elective	1091 (88.4)	131	
Procedure Year			0.018
1992–1997	441 (31.6)	127	
1998–2003	513 (36.7)	101	
2004–2009	443 (31.7)	a	
Surgeon Characteristics			
Surgeon Gender			0.387
Female	12 (1.1)	197	
Male	1058 (98.9)	113	
Surgeon Volume			0.152
Low (< 75 per year)	331 (31.0)	95	
Medium (75–120 per year)	478 (44.8)	126	
High (> 120 per year)	258 (24.2)	116	
Continuous Variables	N	HR	P-value
Age at Diagnosis	1397	1.060	<0.001
Charlson Score	1397	1.283	<0.001
Tumor Size (mm)	1245	1.007	<0.001

^aMedian could not be computed due to censoring.

Table V

Unadjusted and Adjusted Hazard Ratios for Overall Survival According to Lymph Node Recovery Adequacy

Variables	Hazard Ratio (HR)	95% CI	P-value
Unadjusted			
Node Adequacy			
No	Ref		
Yes	0.899	0.754–1.073	0.239
Adjusted ^a			
Node Adequacy			
No	Ref		
Yes	0.711	0.572–0.884	0.002
Cancer Stage			
I	Ref		
II	1.272	0.964–1.677	0.089
III	2.383	1.774–3.201	<0.001
Margins			
Negative	Ref		
Positive	2.643	1.658–4.214	<0.001
Adjuvant Chemotherapy			
Yes	Ref		
No	1.502	1.170–1.928	<0.001
Age at Diagnosis ^b	1.054	1.043–1.066	<0.001
Charlson Score ^b	1.180	1.102–1.264	<0.001

^aVariables entered into the model for forward stepwise selection ($P < 0.05$ to enter) include node adequacy, cancer stage, cancer grade, tumor size, obstruction, perforation, margins, surgery (emergency or elective), adjuvant chemotherapy, procedure year, Charlson score, and age at diagnosis.

^bContinuous variables.

Table VI

Adjuvant Chemotherapy Use and Survival Time in Patients with Adequate and Inadequate Lymph Node Recovery

Lymph Node Recovery	Median Survival (Months)		P-value ^a
	Chemotherapy	No Chemotherapy	
Inadequate			
Stage II	148.3	95.3	0.006
Stage III	92.7	49.3	<0.001
Adequate			
Stage II	159.6	110.0	<0.001
Stage III	121.1	76.4	<0.001

Unadjusted and Adjusted Hazard Ratios for Overall Survival According to Combined Lymph Node Ratio and Lymph Node Recovery Adequacy

Table VII

	Lymph Node Ratio	Lymph Node Recovery	Hazard Ratio (HR)	95% CI	P-value
Unadjusted					
Group I	Low (0)	Adequate	Ref		
Group II	Low (0)	Inadequate	1.151	0.921–1.438	0.217
Group III	High (>0)	Adequate	1.763	1.472–2.110	<0.001
Group IV	High (>0)	Inadequate	2.363	1.770–3.155	<0.001
Adjusted ^a					
Group I	Low (0)	Adequate	Ref		
Group II	Low (0)	Inadequate	1.322	1.015–1.721	0.038
Group III	High (>0)	Adequate	3.112	1.548–6.256	0.001
Group IV	High (>0)	Inadequate	4.143	2.042–8.405	<0.001

^a Adjusted for cancer stage, margins, adjuvant chemotherapy use, age at diagnosis, and Charlson score.