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Number of Lymph Nodes Examined and Prognosis Among Pathologically Lymph Node-Negative Patients After Preoperative Chemoradiation Therapy for Rectal Adenocarcinoma

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Abstract

BACKGROUND—Preoperative chemoradiation for rectal cancer can decrease the number of evaluable lymph nodes. Hence, the prognostic role of lymph node evaluation in patients with rectal cancer who receive preoperative chemoradiation is unclear. The authors of this report evaluated the prognostic impact of the number of lymph nodes examined in patients with rectal cancer who had negative lymph nodes based on the pathologic extent of disease (ypN0) after they received preoperative chemoradiation.

METHODS—Between 1990 and 2004, 372 patients with nonmetastatic rectal adenocarcinoma received preoperative chemoradiation followed by mesorectal excision and had ypN0 disease. The median radiation dose was 45 gray, and 68% of patients received adjuvant chemotherapy.

RESULTS—Patients had a median of 7 lymph nodes examined after preoperative chemoradiation. Compared with patients who had ≤ 7 lymph nodes examined, patients who had > 7 lymph nodes had higher 5-year rates of freedom from relapse (86% vs 72%; log-rank $P = .005$) and cancer-specific survival (95% vs 86%; log-rank $P = .0004$), but no significant difference was observed in the overall survival rate (87% vs 81%; log-rank $P = .07$). Multivariate Cox proportional models demonstrated that patients who had > 7 lymph nodes examined had a significantly lower risk of relapse (hazard ratio [HR], 0.39; $P = .003$) and death from rectal cancer (HR, 0.45; $P = .04$) but a similar risk of all-cause mortality (HR, 0.75; 95% CI, 0.46–1.20; $P = .23$) compared with patients who had ≤ 7 lymph nodes examined.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

CONCLUSIONS—The number of lymph nodes examined was associated independently with disease relapse and cancer-specific survival in patients with rectal cancer who had ypN0 disease after receiving preoperative chemoradiation. Hence, the authors concluded that the number of negative lymph nodes examined may be a prognostic factor in patients with rectal cancer who receive preoperative chemoradiation.

Keywords

rectal cancer; prognostic factors; radiation therapy; lymph nodes

The number of lymph nodes examined is a well established prognostic factor in patients with colorectal cancers.^{1–5} Studies specifically in patients with rectal cancer have demonstrated that the number of retrieved lymph nodes is associated significantly with relapse and survival rates in patients with stage II rectal cancer.^{6,7} The inability to examine a sufficient number of lymph nodes may lead to failure in identifying metastatic lymph nodes and, thus, may portend a worse prognosis. Consequently, the International Union Against Cancer and the American Joint Committee on Cancer recommend examining at least 10 to 14 negative lymph nodes to validate appropriate staging.⁸

Preoperative chemoradiation followed by surgical resection is the current standard of care for patients with stage II and III rectal cancer (T3 or T4 tumor classification and/or positive lymph node status [N1-2]).^{9–14} However, many studies have reported a significant decrease in the number of lymph nodes retrieved from patients with locally advanced rectal cancer who receive preoperative chemoradiation.^{15–19} For example, a study based on the Surveillance, Epidemiology and End Results (SEER) registry demonstrated that only 19% of patients with stage II rectal cancer who received preoperative radiotherapy had at least 12 lymph nodes retrieved for staging.¹⁷

To date, the association between the number of lymph nodes examined and long-term outcome of lymph node-negative patients after neoadjuvant chemoradiation has not been well characterized. Hence, we performed this single-institution, retrospective cohort study to evaluate the prognostic impact of the number of lymph nodes examined in lymph node-negative patients who had received preoperative chemoradiation.

MATERIALS AND METHODS

Eligibility

Between May 1990 and October 2004, 372 patients with newly diagnosed, nonmetastatic adenocarcinoma of the rectum (≤ 12 cm from the anal verge) received preoperative fluorouracil-based chemoradiation followed by mesorectal excision at The University of Texas MD Anderson Cancer Center and had negative lymph node status based on the pathologic extent of disease (ypN0) identified. The clinical and radiation therapy data were reviewed for each patient in this study, and the study was approved by the University of Texas MD Anderson Institutional Review Board.

Pretreatment Evaluation

All patients underwent digital rectal examination, chest x-ray, abdominal and pelvic computed tomography (CT) scans, and endoscopy. Endoscopic ultrasound (EUS) was performed in 84% of patients. Clinical staging was based on the findings from EUS and CT scans. The sixth edition of the American Joint Committee on Cancer TNM system was used for staging.²⁰

Treatment

All 372 patients received preoperative radiation therapy with concurrent chemotherapy followed by mesorectal excision. In total, 245 patients (65.9%) received 45 gray (Gy) of radiation to the pelvis, and 127 patients (34.1%) received 45 Gy to the pelvis along with a sequential or concurrent boost. Radiation therapy was delivered in 1.8-Gy fractions Monday through Friday, typically over 5 or 6 weeks, using 15-MV to 18-MV photons and customized blocking. A 3-field technique (1 posterior field and 2 lateral fields) and an open tabletop (belly board) device for bowel exclusion were used in 99% of patients.

Concurrent chemotherapy was administered with continuous infusion 5-fluorouracil (5-FU) in 287 patients (77.2%), capecitabine in 72 patients (19.4%), sequential 5-FU and capecitabine in 2 patients (0.5%), 5-FU and cisplatin in 6 patients (1.6%), and uracil and tegafur in 5 patients (1.3%). The details of the radiation therapy and chemotherapy regimens were described in an earlier publication.²¹

All patients underwent mesorectal excision, including low anterior resection in 151 patients (40.6%), proctectomy with coloanal anastomosis in 85 patients (22.9%), abdominoperineal resection in 116 patients (31.2%), pelvic exenteration in 18 patients (4.8%), and other types of nonsphincter-sparing resection in 2 patients (0.5%). Adjuvant chemotherapy was received by 254 patients (68.3%). The adjuvant chemotherapy regimens were 5-FU-based therapy in 182 patients (71.7%): 1 patient received 5-FU only, 4 patients received 5-FU and levamisole, 174 patients received 5-FU and leucovorin (15 patients received additional levamisole, and 1 received additional irinotecan), and 3 patients received combined 5-FU, leucovorin, and oxaliplatin. Capecitabine was received by 52 patients (20.5%), uracil and tegafur was received by 5 patients (2.0%), and 18 patients (7.1%) received an unknown adjuvant chemotherapy agent. The median follow-up was 7.6 years (range, from 2 months to 18.6 years).

After surgery, operative pathologic specimens were reviewed by gastrointestinal pathologists at The University of Texas MD Anderson Cancer Center who determined the tumor pathology, pathologic stage, and number of retrieved lymph nodes. For the purposes of the current study, information on the number of retrieved lymph nodes was obtained from the pathology reports at the time of surgery.

Statistical Analysis

All statistical analyses were carried out using the SAS software package (version 9.2; SAS Institute, Inc., Cary, NC). The patients were divided into 2 subgroups based on the median number of lymph nodes retrieved (≤ 7 lymph nodes retrieved vs > 7 lymph nodes retrieved). In a separate analysis, the patients were divided into 4 subgroups (≤ 3 lymph nodes retrieved, 3–7 lymph nodes retrieved, 8–12 lymph nodes retrieved, and > 12 lymph nodes retrieved) based on the quartile distributions of the numbers of lymph nodes examined. Chi-square tests or Fisher exact tests were used to determine the significance of the association between subgroups of patients and the following categorical variables: sex, race, neoadjuvant chemotherapy type, year of surgery (1990–1994, 1995–1999, or 2000–2004), type of surgery (sphincter-sparing or non-sphincter-sparing), anal canal involvement, diagnostic histology, clinical T classification (cT), clinical lymph node classification (N), pathologic tumor stage, lympho-vascular invasion, perineural invasion, downstaging (cT classification $>$ ypT stage), receipt of adjuvant chemotherapy, local recurrence/distant metastasis, and vital status. The Kruskal-Wallis test was used to compare the median levels and overall distributions of the following continuous variables: age, tumor size, and distance from the anal verge.

Survival and the time to recurrence/distant metastasis within each subgroup of patients were estimated using the Kaplan-Meier method.²² The length of follow-up was measured from the time of surgery to either the time of local recurrence/distant metastasis (for assessing the time to relapse), death from rectal cancer (for cancer-specific survival), death from any cause (for overall survival), or last contact. The log-rank test²³ was used for univariate comparison of risk factors between subgroups of patients. A Cox proportional hazards model²⁴ was used to compute univariate and multivariate hazard ratios (HRs) comparing prognostic risk factors between patients who had ≤ 7 lymph nodes retrieved and patients who had > 7 lymph nodes retrieved.

RESULTS

Among the 372 patients in this study, the clinical tumor classification was as follows: T2 (tumor invading the muscularis propria) in 20 patients (5.4%), T3 (tumor invading through the muscularis propria) in 313 patients (84.1%), T4 (tumor invading other organs or structures) in 36 patients (9.7%), and unknown in 3 patients (0.8%). The clinical lymph node classification was N0 (no regional lymph node metastasis) in 195 patients (52.4%), N1 (metastasis in 1–3 regional lymph nodes) in 167 patients (44.9%), N2 (metastasis in ≥ 4 regional lymph nodes) in 3 patients (0.8%), and unknown in 7 patients (1.9%). The pathologic tumor classification was as follows: well differentiated adenocarcinoma in 22 patients (5.9%), moderately differentiated adenocarcinoma in 274 patients (73.7%), poorly differentiated adenocarcinoma in 18 patients (4.8%), and unknown in 58 patients (15.6%). The median number of lymph nodes examined was 7 (range, 0–40 lymph nodes examined).

The median follow-up was 8.4 years for patients who had ≤ 7 lymph nodes retrieved (20 patients were lost to follow-up, which was defined by a lack of patient contact in the last 2 years) and 6.8 years for patients who had > 7 lymph nodes retrieved (17 patients were lost to follow-up). Table 1 lists the baseline characteristics of the 372 patients according to the number of lymph nodes retrieved (≤ 7 vs > 7). Patients who had ≤ 7 lymph nodes retrieved were more likely to 1) receive concurrent 5-FU (89.4% vs 64.7%) than capecitabine (6.9% vs 32.1%; $P < .0001$), 2) not receive a radiation boost (21.8% vs 46.7%; $P < .0001$), 3) undergo nonsphincter-sparing surgery (43.6% vs 29.4%; $P = .004$), 4) have extension to the anal canal (38.8% vs 22.3%; $P = .0005$), 5) have a larger tumor size ($P = .04$), and 6) have clinical N0 lymph node status (59.6% vs 45.1%; $P = .02$) compared with patients who had ≥ 7 lymph nodes examined. In addition, patients who had ≤ 7 lymph nodes examined were less likely undergo surgery after 2000 (12.2% vs 44.6%; $P < .0001$) and were less likely to receive adjuvant chemotherapy (57.8% vs 82.2%; $P < .0001$) compared with those who had > 7 lymph nodes examined. Between the 2 subgroups of patients, there was no significant difference in the distributions of sex, age, race, clinical T classification, pathologic T stage, lymphovascular invasion, perineural invasion, or downstaging status.

During follow-up, 16 patients developed local recurrences (4.3%). Of these, 13 patients also had distant metastasis (4 patients had both local recurrence and distant metastasis detected at the same time, 8 patients had local recurrence as the first site of failure then metastasis in 1 year, and 1 patient had metastasis detected first and local recurrence detected later). Only 3 patients had a local recurrence without distant metastasis during follow-up. In total, 69 patients (18.5%) developed distant metastasis (13 patients also had a local recurrence, as described above), 111 patients (29.7%) patients died, and 46 patients (12.3%) had documented death from rectal cancer. It is noteworthy that, because of the small number of patients with local recurrence only, patients who had local recurrence and/or distant metastasis were grouped together in subsequent analyses.

The estimated 5-year rates of freedom from relapse/metastasis, cancer-specific survival, and overall survival according to the number of lymph nodes examined are listed in Table 2. The Kaplan-Meier curves for freedom from relapse/metastasis, cancer-specific survival, and overall survival according to the number of lymph nodes examined (≤ 7 vs > 7), along with the number of patients at risk and 95% Hall-Wellner confidence bands, are provided in Figures 1 through 3. Compared with patients who had > 7 lymph nodes examined, patients who had ≤ 7 lymph nodes examined had significantly lower rates of freedom from relapse/metastasis (log-rank $P = .0045$) and cancer-specific survival (log-rank $P = .0004$). There was no significant difference in overall survival between the 2 patient groups ($P = .0674$), although there was a trend toward lower overall survival in patients who had ≤ 7 lymph nodes examined. Similar results were observed when the patients were divided into 4 subgroups based on quartile distributions according to the number of lymph nodes retrieved (0–3 lymph nodes, 4–7 lymph nodes, 8–12 lymph nodes, or > 12 lymph nodes) in the study population. Patients in the fourth quartile (> 12 lymph nodes retrieved) had higher rates of 5-year freedom from relapse/metastasis and cancer-specific survival compared with patients in the other quartiles.

A Cox proportional hazards model was used to estimate HRs of disease relapse/metastasis, cancer-specific death, and all-cause mortality in comparing patients who had > 7 lymph nodes retrieved with patients who had ≤ 7 lymph nodes retrieved. Patients who had > 7 lymph nodes retrieved had a 50% lower risk of local disease relapse or distant metastasis (HR, 0.50; 95% confidence interval [CI], 0.31–0.81; $P = .005$) and a 70% lower risk of cancer-specific death (HR, 0.30; 95% CI, 0.15–0.61; $P = .0008$) over the follow-up period compared with patients who had ≤ 7 lymph nodes examined (Table 3). It is noteworthy that patients who had > 7 lymph nodes retrieved also had an approximately 68% lower risk of local recurrence with or without distant metastasis (HR, 0.32; 95% CI, 0.10–1.0; $P = .05$). However, it should be noted that 13 of the 16 patients who developed a local recurrence also had distant metastasis, as described above.

The results remained significant after adjusting for age, sex, race, clinical tumor and lymph node classification, pathologic tumor stage, downstaging, receipt of adjuvant chemotherapy, distance from the anal verge, and year of surgery in the multivariate model. Further adjustments for radiation dose, tumor size, anal canal involvement, and type of neoadjuvant chemotherapy did not change the results significantly (data not shown), and these variables were not included in subsequent multivariate models. Tumor histology was not included in the multivariate model because of a large percentage of missing data and also because the majority of patients had moderately differentiated adenocarcinoma. The 2 groups of patients did not have a statistically significant difference in the risk of all-cause mortality in either univariate analysis (HR, 0.70; 95% CI, 0.47–1.03; $P = .07$) or multivariate analysis (HR, 0.75; 95% CI, 0.46–1.20; $P = .23$). Among the covariates that were adjusted in the multivariate model, only black race and distance from the anal verge were associated independently with disease relapse/metastasis (Table 4).

Comparable results were obtained when the patients were divided into 4 subgroups based on quartile distributions according to the number of lymph nodes retrieved. Compared with patients in the first quartile (0–3 lymph nodes), patients in the third quartile (8–12 lymph nodes) and the fourth quartile (> 12 lymph nodes) had significantly lower risks of disease recurrence or distant metastasis in univariate analysis (HR, 0.38 [$P = .006$] and HR, 0.43 [$P = .02$], respectively) and in multivariate analysis (HR, 0.39 [$P = .02$] and HR, 0.34 [$P = .01$] respectively). There was no statistically significant difference in the risk of disease recurrence or metastasis between patients in the first (0–3 lymph nodes) and second (4–7 lymph nodes) quartiles (data not shown). Similarly, patients in the fourth quartile had a significantly reduced risk of cancer-specific mortality (HR, 0.25; $P = .05$) and all-cause

mortality (HR, 0.51; $P = .03$) compared with patients in the first quartile in univariate analysis, although the results were not statistically significant in the multivariate models (data not shown).

DISCUSSION

In the current study, we evaluated the prognostic impact of the number of lymph nodes retrieved from patients with ypN0 rectal cancer who received preoperative chemoradiation therapy followed by mesorectal excision. The number of lymph nodes examined was associated independently with the rates of cancer-specific survival and freedom from disease relapse or metastasis in both univariate and multivariate proportional hazard models. Patients who had ≤ 7 lymph nodes examined had a higher rate of disease relapse or metastasis and a lower rate of cancer-specific survival compared with patients who had >7 lymph nodes examined.

Lymph node retrieval and assessment is critical in rectal cancer staging and can impact further interventional decisions, such as adjuvant chemotherapy. A positive lymph node is more likely to be identified if more lymph nodes are examined, and patients with lymph node-negative colorectal cancer, on average, have fewer lymph nodes examined than patients with lymph node-positive disease.^{7,25} The National Cancer Institute guidelines have recommended a minimum of 12 lymph nodes for adequately staging a lymph node-negative colorectal cancer.^{8,26} However, the number of lymph nodes retrieved can vary significantly, depending on the anatomic site, with lower yield in resected rectal cancer specimens and higher yield in colon cancer specimens.^{27,28}

Preoperative radiation (with or without chemotherapy) can decrease the number of retrieved lymph nodes substantially, likely because of lymph node atrophy, fibrosis, and lymphocyte depletion.²⁹ Studies have demonstrated that chemoradiation significantly decreases the number of lymph nodes retrieved in surgical rectal specimens.^{16,17,19,29} A study based on the SEER registry indicated that patients who received preoperative radiation therapy had an average of 7 lymph nodes retrieved compared with 10 lymph nodes from patients who did not receive preoperative radiation.¹⁷ Similar results were observed in another study in which an average of 13 lymph nodes were retrieved from patients who received preoperative radiation, and an average of 19 lymph nodes were retrieved from patients who did not receive preoperative radiation.¹⁶ Rullier et al also demonstrated that, compared with patients who did not receive preoperative chemoradiation, those who did had a decreased mean number of lymph nodes retrieved (17 lymph nodes vs 13 lymph nodes) and a decreased mean number of positive lymph nodes (2.3 lymph nodes vs 1.2 lymph nodes).¹⁹ Taflampas et al reported that preoperative chemoradiation did not reduce the overall number of lymph nodes retrieved but did increase the percentage of patients with <12 lymph nodes examined.³⁰ In contrast, a study of selected patients who were treated on the German rectal cancer trial indicated that extensive pathologic evaluation may enable the detection of high numbers of lymph nodes (median, 30 lymph nodes) even after preoperative chemoradiation.³¹

Aside from preoperative chemoradiation, other factors, such as the extent of surgery, thorough pathologic assessment, tumor location, histologic grade, and other patient-related factors, can have a significant impact on the number of lymph nodes retrieved.^{32–35} Among patients who received preoperative radiation therapy (5×5 Gy), more lymph nodes were retrieved after low anterior resection than after abdominoperineal resection.³⁶ Lymph node yield also differed significantly between laboratories and pathologists. It has been demonstrated that the fat-clearance method of lymph node harvest has a significant impact on the number of lymph nodes examined and lymph node staging among patients with

lymph node-negative rectal cancer after neoadjuvant chemoradiation compared with traditional methods.³⁷ Injection of the inferior mesenteric artery with methylene blue dye also can increase lymph node harvest.³⁸ In addition, among lymph node-negative patients, specimens from tumors that measured >5 cm in greatest dimension contained more lymph nodes than specimens from tumors that measured <2 cm (10.0 lymph nodes vs 4.4 lymph nodes).³⁶ Lymph node-negative patients who had well differentiated tumors with extensive lymphoid reaction also had an increased number of lymph nodes retrieved, although histologic grade did not have an impact on the number of lymph nodes retrieved. Older patients typically have fewer lymph nodes harvested, probably secondary to reduced inflammatory and immunologic reactions to cancer.^{28,35,39} However, of the above factors, only patient age, tumor size, and type of surgical procedure were associated significantly with the number of lymph nodes retrieved among lymph node-negative patients in multivariate analysis.³⁶

Previous studies that evaluated the association between the number of lymph nodes examined and prognosis in patients with rectal cancer after preoperative chemoradiation reported various results. Luna-Perez et al conducted a study on 210 patients with either lymph node-negative or lymph node-positive rectal cancer who received preoperative chemoradiation, and patients in that study who had ≥ 11 lymph nodes retrieved had a significantly lower rate of local recurrence and a significantly higher rate of overall survival compared with patients who had <11 lymph nodes retrieved.⁴⁰ However, Rullier et al reported that the number of lymph nodes retrieved was not associated with disease-free survival or overall survival among 198 patients with pathologically lymph node-negative disease who received preoperative chemoradiation.¹⁹ Moreover, Kim et al observed that, among patients who received preoperative chemoradiation, the number of lymph nodes retrieved was not associated significantly with recurrence or survival in 150 patients with lymph node-negative rectal cancer.⁴¹ However, those studies had smaller cohorts compared with the current study and, thus, may have had lower power to detect an association. To our knowledge, the current study is the largest study to specifically evaluate the association between the number of lymph nodes examined and prognosis among patients with pathologically lymph node-negative rectal cancer after preoperative chemoradiation.

Low lymph node yield can be secondary to differences in surgical or pathologic approach, intrinsic tumor factors, and patient characteristics, as discussed above. Tumor understaging because of low lymph node yield may contribute to decreased time to disease relapse and shortened cancer-specific survival. Lymph node-negative patients with low lymph node yield may have been identified as lymph node-positive if more lymph nodes had been examined. Although only patients who had ypN0 disease were included in our study, 46% of these patients were lymph node-positive on preoperative staging studies. The large proportion of clinically lymph node-positive patients implies that some patients may have been under-staged on pathologic staging.

The results from this study need to be interpreted with caution. Because data on histologic grade, lympho-vascular invasion, and perineural invasion were incomplete, they were not included in the multivariate analysis. Even with the inclusion of many possible confounders, it is worth noting that residual confounding still may be present. Because many of the variables in the multivariate model are correlated, collinearity of those variables may make it unnecessary to include all of them in the multivariate model. The study was conducted on patients who received treatment over a 14-year period, and it is possible that surgical and pathologic techniques changed over that time. A lack of data on patients who were lost to follow-up also potentially may bias the study results. It is noteworthy that the proportion of patients who had >7 lymph nodes examined increased significantly over the years of the study period. Consequently, the median follow-up was longer for patients who had ≤ 7

lymph nodes retrieved, leading to more time for them to develop recurrence than the other group. However, after adjusting for year of surgery, the observed results remained statistically significant. In addition, there were considerable differences in the 5-year freedom from recurrence/distant metastasis and survival rates between the 2 patient groups (Table 2), supporting the conclusion that patients who had fewer lymph nodes retrieved had a poorer prognosis than patients who had more lymph nodes retrieved, even if both groups had a fixed length of follow-up. Furthermore, when we performed a multivariate analysis comparing recurrence/distant metastasis and survival rates between the 2 groups of patients based only on events that occurred within 5 years of follow-up, the differences between the 2 groups remained statistically significant (data not shown).

In conclusion, the number of lymph nodes examined was associated independently with disease relapse and cancer-specific survival in patients with ypN0 rectal cancer who received preoperative chemoradiation. Although high-quality surgery and thorough pathologic examination might improve lymph node yield and provide more accurate staging after preoperative chemoradiation, many other factors, including patient-specific and tumor-specific factors, also may affect the number of lymph nodes examined. Numerous studies have demonstrated decreased lymph node yield after preoperative chemoradiation therapy. Many clinicians may be left with imperfect pathologic lymph node staging from a limited number of examined lymph nodes in patients with rectal cancer who receive preoperative chemoradiation. Thus, it may be prudent to incorporate information on the number of lymph nodes examined in patients with negative lymph node into clinical decision-making. Risk stratification and management based on the number of lymph nodes may help guide clinicians in counseling patients about their prognosis, making decisions on adjuvant chemotherapy, and potentially optimizing disease control and survival.

References

1. Caplin S, Cerottini JP, Bosman FT, Constanda MT, Givel JC. For patients with Dukes' B (TNM stage II) colorectal carcinoma, examination of 6 or fewer lymph nodes is related to poor prognosis. *Cancer*. 1998; 83:666–672. [PubMed: 9708929]
2. Ciani F, Palomba A, Boddi V, et al. Lymph node recovery from colorectal tumor specimens: recommendation for a minimum number of lymph nodes to be examined. *World J Surg*. 2002; 26:384–389. [PubMed: 11865379]
3. Sarli L, Bader G, Iusco D, et al. Number of lymph nodes examined and prognosis of TNM stage II colorectal cancer. *Eur J Cancer*. 2005; 41:272–279. [PubMed: 15661553]
4. Chang GJ, Rodriguez-Bigas MA, Skibber JM, Moyer VA. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. *J Natl Cancer Inst*. 2007; 99:433–441. [PubMed: 17374833]
5. Le Voyer TE, Sigurdson ER, Hanlon AL, et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of Intergroup Trial INT-0089. *J Clin Oncol*. 2003; 21:2912–2919. [PubMed: 12885809]
6. Kim YW, Kim NK, Min BS, Lee KY, Sohn SK, Cho CH. The influence of the number of retrieved lymph nodes on staging and survival in patients with stage II and III rectal cancer undergoing tumor-specific mesorectal excision. *Ann Surg*. 2009; 249:965–972. [PubMed: 19474683]
7. Tepper JE, O'Connell MJ, Niedzwiecki D, et al. Impact of number of nodes retrieved on outcome in patients with rectal cancer. *J Clin Oncol*. 2001; 19:157–163. [PubMed: 11134208]
8. Edge, SB.; Byrd, DR.; Compton, CC.; Fritz, AG.; Greene, FL.; Trotti, A., editors. *AJCC Cancer Staging Manual*. 7. New York: Springer; 2010.
9. Bosset JF, Calais G, Mineur L, et al. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results—EORTC 22921. *J Clin Oncol*. 2005; 23:5620–5627. [PubMed: 16009958]
10. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med*. 2006; 355:1114–1123. [PubMed: 16971718]

11. Das P, Crane CH. Preoperative and adjuvant treatment of localized rectal cancer. *Curr Oncol Rep*. 2006; 8:167–173. [PubMed: 16618380]
12. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*. 2004; 351:1731–1740. [PubMed: 15496622]
13. Gerard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *J Clin Oncol*. 2006; 24:4620–4625. [PubMed: 17008704]
14. Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. *J Clin Oncol*. 2009; 27:5124–5130. [PubMed: 19770376]
15. Sermier A, Gervaz P, Egger JF, et al. Lymph node retrieval in abdominoperineal surgical specimen is radiation time-dependent [serial online]. *World J Surg Oncol*. 2006; 4:29. [PubMed: 16749931]
16. Wichmann MW, Muller C, Meyer G, et al. Effect of preoperative radiochemotherapy on lymph node retrieval after resection of rectal cancer. *Arch Surg*. 2002; 137:206–210. [PubMed: 11822961]
17. Baxter NN, Morris AM, Rothenberger DA, Tepper JE. Impact of preoperative radiation for rectal cancer on subsequent lymph node evaluation: a population-based analysis. *Int J Radiat Oncol Biol Phys*. 2005; 61:426–431. [PubMed: 15667963]
18. Nagtegaal ID, van de Velde CJ, van der Worp E, Kapiteijn E, Quirke P, van Krieken JH. Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. *J Clin Oncol*. 2002; 20:1729–1734. [PubMed: 11919228]
19. Rullier A, Laurent C, Capdepont M, et al. Lymph nodes after preoperative chemoradiotherapy for rectal carcinoma: number, status, and impact on survival. *Am J Surg Pathol*. 2008; 32:45–50. [PubMed: 18162769]
20. American Joint Committee on Cancer (AJCC). Colon and Rectum. In: Greene, FL.; Page, DL.; Fleming, ID., et al., editors. *AJCC Cancer Staging Handbook*. 6. New York: Springer-Verlag; 2002. p. 127-138.
21. Das P, Skibber JM, Rodriguez-Bigas MA, et al. Predictors of tumor response and downstaging in patients who receive preoperative chemoradiation for rectal cancer. *Cancer*. 2007; 109:1750–1755. [PubMed: 17387743]
22. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958; 53:457–481.
23. Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J R Stat Soc A*. 1972; 135:185–206.
24. Cox DR. Regression models and life tables. *J R Stat Soc B*. 1972; 34:187–220.
25. Wong JH, Severino R, Honnebler MB, Tom P, Namiki TS. Number of nodes examined and staging accuracy in colorectal carcinoma. *J Clin Oncol*. 1999; 17:2896–2900. [PubMed: 10561368]
26. Nelson H, Petrelli N, Carlin A, et al. Guidelines 2000 for colon and rectal cancer surgery. *J Natl Cancer Inst*. 2001; 93:583–596. [PubMed: 11309435]
27. Canessa CE, Badia F, Fierro S, Fiol V, Hayek G. Anatomic study of the lymph nodes of the mesorectum. *Dis Colon Rectum*. 2001; 44:1333–1336. [PubMed: 11584211]
28. Shen SS, Haupt BX, Ro JY, Zhu J, Bailey HR, Schwartz MR. Number of lymph nodes examined and associated clinicopathologic factors in colorectal carcinoma. *Arch Pathol Lab Med*. 2009; 133:781–786. [PubMed: 19415953]
29. Marks JH, Valsdottir EB, Rather AA, Nweze IC, Newman DA, Chernick MR. Fewer than 12 lymph nodes can be expected in a surgical specimen after high-dose chemoradiation therapy for rectal cancer. *Dis Colon Rectum*. 2010; 53:1023–1029. [PubMed: 20551754]
30. Taflampas P, Christodoulakis M, Gourtsoyianni S, Leventi K, Melissas J, Tsiatsis DD. The effect of preoperative chemoradiotherapy on lymph node harvest after total mesorectal excision for rectal cancer. *Dis Colon Rectum*. 2009; 52:1470–1474. [PubMed: 19617762]
31. Sprenger T, Rothe H, Homayounfar K, et al. Preoperative chemoradiotherapy does not necessarily reduce lymph node retrieval in rectal cancer specimens—results from a prospective evaluation with extensive pathological work-up. *J Gastrointest Surg*. 2010; 14:96–103. [PubMed: 19830503]

32. Sigurdson ER. Lymph node dissection: is it diagnostic or therapeutic? *J Clin Oncol*. 2003; 21:965–967. [PubMed: 12637458]
33. Thorn CC, Woodcock NP, Scott N, Verbeke C, Scott SB, Ambrose NS. What factors affect lymph node yield in surgery for rectal cancer? *Colorectal Dis*. 2004; 6:356–361. [PubMed: 15335370]
34. Gorog D, Nagy P, Peter A, Perner F. Influence of obesity on lymph node recovery from rectal resection specimens. *Pathol Oncol Res*. 2003; 9:180–183. [PubMed: 14530812]
35. Guillem JG, Diaz-Gonzalez JA, Minsky BD, et al. cT3N0 rectal cancer: potential overtreatment with preoperative chemoradiotherapy is warranted. *J Clin Oncol*. 2008; 26:368–373. [PubMed: 18202411]
36. Mekenkamp LJ, van Krieken JH, Marijnen CA, van de Velde CJ, Nagtegaal ID. Lymph node retrieval in rectal cancer is dependent on many factors—the role of the tumor, the patient, the surgeon, the radiotherapist, and the pathologist. *Am J Surg Pathol*. 2009; 33:1547–1553. [PubMed: 19661781]
37. Wang H, Safar B, Wexner SD, Denoya P, Berho M. The clinical significance of fat clearance lymph node harvest for invasive rectal adenocarcinoma following neoadjuvant therapy. *Dis Colon Rectum*. 2009; 52:1767–1773. [PubMed: 19966611]
38. Kerwel TG, Spatz J, Anthuber M, Wunsch K, Arnholdt H, Markl B. Injecting methylene blue into the inferior mesenteric artery assures an adequate lymph node harvest and eliminates pathologist variability in nodal staging for rectal cancer. *Dis Colon Rectum*. 2009; 52:935–941. [PubMed: 19502859]
39. Baxter NN, Virnig DJ, Rothenberger DA, Morris AM, Jessurun J, Virnig BA. Lymph node evaluation in colorectal cancer patients: a population-based study. *J Natl Cancer Inst*. 2005; 97:219–225. [PubMed: 15687365]
40. Luna-Perez P, Rodriguez-Ramirez S, Alvarado I, Gutierrez de la Barrera M, Labastida S. Prognostic significance of retrieved lymph nodes per specimen in resected rectal adenocarcinoma after preoperative chemoradiation therapy. *Arch Med Res*. 2003; 34:281–286. [PubMed: 12957524]
41. Kim YW, Kim NK, Min BS, et al. The prognostic impact of the number of lymph nodes retrieved after neoadjuvant chemoradiotherapy with mesorectal excision for rectal cancer. *J Surg Oncol*. 2009; 100:1–7. [PubMed: 19418495]

Figure 1.

Freedom from relapse or metastasis is illustrated in patients with rectal cancer according to the number of lymph nodes retrieved (≤ 7 vs > 7).

Figure 2.

Cancer-specific survival is illustrated in patients with rectal cancer according to the number of lymph nodes retrieved (≤ 7 vs >7).

Figure 3. Overall survival is illustrated in patients with rectal cancer according to the number of lymph nodes retrieved (≤ 7 vs > 7).

Table 1

General Characteristics of the Study Population

	No. of Patients (%)		
Characteristic	≤7 Lymph Nodes, n = 188	>7 Lymph Nodes, n = 184	<i>P</i> ^a
Sex			
Women	62 (33)	72 (39.1)	.22
Men	126 (67)	112 (60.9)	
Race			
White	147 (78.2)	146 (79.4)	.88
Hispanic	19 (10.1)	15 (8.2)	
Black	14 (7.5)	13 (7.1)	
Other	8 (4.3)	10 (5.4)	
Age: Median [range], y	59.0 [23.1–87.8]	57.9 [23.9–79.3]	.71
Total radiation dose, cGy			
4500	147 (78.2)	98 (53.3)	<.0001
>4500 ^b	41 (21.8)	86 (46.7)	
Neoadjuvant chemotherapy type			
Capecitabine	13 (6.9)	59 (32.1)	<.0001
5-FU and capecitabine	1 (0.5)	1 (0.5)	
5-FU	168 (89.4)	119 (64.7)	
5-FU and cisplatin	5 (2.7)	1 (0.5)	
UFT	1 (0.5)	4 (2.2)	
Year of surgery			
1990–1994	80 (42.6)	24 (13)	<.0001
1995–1999	85 (45.2)	78 (42.4)	
2000–2004	23 (12.2)	82 (44.6)	
Surgery type			
Sphincter-sparing	106 (56.4)	130 (70.7)	.004
Nonsphincter-sparing	82 (43.6)	54 (29.4)	
Extension to anal canal	73 (38.8)	41 (22.3)	.0005
Tumor size: Median [range], cm	5 [1.5–15]	5 [1–11]	.04
Tumor distance from anal verge: Median (range), cm	5 [0–12]	5 [0–12]	.04
Diagnostic histology			
Well differentiated adenocarcinoma	11 (5.9)	11 (6)	.04
Moderately differentiated adenocarcinoma	128 (68.1)	146 (79.4)	
Poorly differentiated adenocarcinoma	10 (5.3)	8 (4.4)	
Unknown	39 (20.7)	19 (10.3)	
Clinical tumor classification			
cT2	11 (5.9)	9 (4.9)	.92
cT3	157 (83.5)	156 (84.8)	
cT4	18 (9.6)	18 (9.8)	
Unknown	2 (1.1)	1 (5.4)	

Characteristic	No. of Patients (%)		<i>P</i> ^a
	≤7 Lymph Nodes, n = 188	>7 Lymph Nodes, n = 184	
Clinical lymph node classification			
N0	112 (59.6)	83 (45.1)	.02
N1	73 (38.8)	94 (51.1)	
N2	1 (0.5)	2 (1.1)	
Unknown	2 (1.1)	5 (2.7)	
Lymphovascular invasion			
Present	7 (3.7)	10 (5.41)	.07
Absent	113 (60.1)	89 (48.4)	
Unknown	68 (36.2)	85 (46.2)	
Perineural invasion			
Present	6 (3.2)	8 (4.4)	.68
Absent	47 (25)	40 (21.7)	
Unknown	135 (71.8)	136 (73.9)	
Pathologic tumor classification			
T0/in situ	48 (25.5)	39 (21.2)	.67
T1	12 (6.4)	15 (8.2)	
T2	66 (35.1)	60 (32.6)	
T3	51 (27.1)	61 (33.2)	
T4	10 (5.3)	7 (3.8)	
Unknown	1 (0.5)	2 (1.1)	
Downstaging			
Downstaged	124 (66.7)	119 (65.8)	.70
Unchanged	59 (31.7)	61 (33.7)	
Upstaged	3 (1.6)	1 (0.6)	
Received adjuvant chemotherapy	107 (57.8)	147 (82.2)	<.0001

cGy indicates centigrays; 5-FU, 5-fluorouracil; UFT, uracil and tegafur.

^aThe chi-square test and the Fisher test were used to compare the distribution of categorical variables; the Kruskal-Wallis test was used to compare median levels of continuous variables.

^b5040, 5240, and 5860.

Five-Year Freedom From Recurrence/Distant Metastasis and Survival Rates According to the Number of Lymph Nodes Examined

Table 2

Analysis	Percentage of Patients (No. at Risk)				
	By Median No.		By Quartile		
	≤7 Lymph Nodes	>7 Lymph Nodes	0–3 Lymph Nodes	4–7 Lymph Nodes	8–12 Lymph Nodes >12 Lymph Nodes
Free from recurrence and metastasis ^a	72.2 (185)	85.8 (183)	67.6 (84)	75.9 (101)	86 (95) 85.7 (88)
Cancer-specific survival ^b	85.7 (188)	95.2 (184)	83.3 (87)	87.7 (101)	95.1 (96) 95.3 (88)
Overall survival	81 (188)	86.9 (184)	79.9 (87)	81.9 (101)	86.8 (96) 87.1 (88)

^a An event was defined as local recurrence or distant metastasis; the date of recurrence or death was used as the censoring date.

^b An event was defined as death from rectal cancer; deaths from other causes were censored, and the date of death was used as the censoring date.

Table 3

Univariate and Multivariate Hazard Ratios of Relapse/Metastasis and Survival in Patients With Rectal Cancer: ≥ 7 Lymph Nodes Retrieved Versus < 7 Lymph Nodes Retrieved

Analysis	HR	95% CI	P
Univariate			
Recurrence/distant metastasis	0.50	0.31–0.81	.005
Cancer-specific death	0.30	0.15–0.61	.0008
All-cause mortality	0.70	0.47–1.03	.07
Multivariate^a			
Recurrence/distant metastasis	0.39	0.21–0.73	.003
Cancer-specific death	0.45	0.21–0.98	.04
All-cause mortality	0.75	0.46–1.20	.23

HR indicates hazard ratio; CI, confidence interval.

^aMultivariate analyses were adjusted for age, sex, race, clinical tumor and lymph node classification, pathologic tumor classification, downstaging, distance from anal verge, adjuvant chemotherapy, and year of surgery.

Table 4

Multivariate Hazard Ratios for Disease Recurrence/Distant Metastasis, by Patient and Tumor Characteristics

Characteristic	HR	95% CI	P
No. of lymph nodes			
≥7 vs <7	0.39	0.21–0.73	.003
Age			
≥60 y vs <60 y	0.61	0.35–1.06	.08
Sex			
Men vs women	0.93	0.55–1.57	.78
Race (reference, white)			
Black	3.10	1.54–6.26	.002
Hispanic	0.84	0.35–2.05	.70
Other	2.09	0.71–6.18	.18
Clinical tumor classification (reference, T2)			
cT3	0.65	0.17–2.54	.53
cT4	1.04	0.12–8.96	.97
Clinical lymph node classification (reference, N0)			
N1	0.88	0.52–1.51	.65
Pathologic tumor classification (reference, T0)			
T1	1.08	0.21–5.50	.93
T2	1.77	0.75–4.17	.19
T3	3.71	0.81–16.96	.09
T4	2.41	0.18–31.97	.51
Downstaging (reference, downstaged)			
Unchanged	1.48	0.37–5.95	.58
Upstaged	6.69	0.37–121.49	.20
Distance from anal verge			
>5 cm vs ≤5 cm	0.55	0.33–0.92	.02
Adjuvant chemotherapy			
Yes vs no	0.98	0.55–1.75	.95
Year of surgery (reference, 1990–1994)			
1995–1999	1.35	0.73–2.53	.34
2000–2004	1.41	0.64–3.15	.40

HR indicates hazard ratio; CI, confidence interval.

^a Analyses were mutually adjusted for the number of lymph nodes retrieved (≥7 vs <7), age, sex, race, clinical T and N classification, pathologic tumor classification, downstaging, distance from anal verge, adjuvant chemotherapy, and year of surgery.