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ORIGINAL ARTICLE

The total number of lymph nodes harvested is associated with better survival in stages II and III colorectal cancer

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Abstract
Background Lymph node status is important in staging colorectal cancer (CRC). Presence of metastatic nodes differentiates stage III from stage II. The role of adjuvant therapy is still unclear in stage II CRC. Inadequate node sampling may result in inaccurate staging.
Method Records of 131 patients with stages II and III CRC who underwent curative resection, having five or more lymph nodes harvested from the specimen, were prospectively followed up and analyzed. The Kaplan–Meier method was used to analyze survival, based on groups of serially ascending values of lymph nodes harvested. Regression analysis was performed by Cox proportional hazards ratio model with right-censored CRC survival data at a 10 % significance level. The effect of nodal harvest on survival was adjusted for age, sex, preoperative carcinoembryonic antigen (CEA) level, neoadjuvant chemoradiation, pathological tumor stage, histological type, differentiation, margin positivity, angioinvasion, perineural invasion, and lymphovascular infiltration.
Results The total population showed improved survival with 14 or more nodes harvested ($p=0.005$). For both rectal ($n=83$; $p=0.03$) and colon cancers ($n=46$; $p=0.08$), most significant survival benefits were seen with over 14 nodes harvested, irrespective of the stage. With multiple regression analysis, advanced age ($p=0.003$), male sex ($p=0.017$), lymphovascular infiltration ($p=0.015$), and preoperative CEA levels ($p=0.096$) were found to be other significant factors. The lymph node effect remained significant (HR=0.19, $p=0.004$) after adjusting for the above factors.
Conclusion A lymph node harvest of 14 or more resulted in better survival outcome from CRC in this population. Staging of the disease could be accurate with increased nodal harvesting.

Keywords Colorectal cancer · Curative resection · Lymph node harvest · Neoadjuvant chemotherapy · Surgical outcome · Survival

Background

Survival in colorectal cancer (CRC) is related to the stage of disease at diagnosis. There is uncertainty as to why some stage II cancers behave as stage III cancers [1]. The use of adjuvant chemotherapy in stage III disease is clearly established and has a proven survival benefit [2, 3]. The role of such therapy in stage II disease is yet to reach consensus [4–6]. The most critical determinant of disease stage is the lymph node status [7]. Presence of tumor in lymph nodes will differentiate stage III from stage II disease. Several authors have shown increased node positivity ratios and improved survival with an increase in the total lymph node yield [8–12]. The National Comprehensive Cancer Network (NCCN) and the American College of Pathologists (ACP) recommend analysis of a minimum of 12 lymph nodes for accurate staging [13, 14]. This consensus, though accepted around the world, is not based on survival studies. A suboptimal lymph node harvest may erroneously categorize stage III disease as stage II and preclude the benefit of adjuvant chemotherapy. Despite the importance and implications of adequate node evaluation, population-based studies have shown that only between 22 % and 37 % of cancers have an adequate number of nodes analyzed [15, 16]. This study prospectively analyzed patients with stages II and III CRC to identify the survival benefit of the total number of lymph nodes harvested.

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Methods

One hundred and thirty-one patients with stages II and III CRC who underwent curative resection between 1997 and 2007 and prospectively followed up for a minimum of 3 years after operation were analyzed. Collection of data was proforma based. Ethical approval was obtained for the study from the ethics review committee of the Faculty of Medicine at the University of Kelaniya, Sri Lanka. Patients with stage III cancer and some with stage II cancer having poor prognostic features received adjuvant chemotherapy with standard regimens (cisplatin or irinotecan based). All curative resections were performed by the same team to standard protocol. Specimens were analyzed by a single pathologist. Specimens were dissected after 10 % formaldehyde fixation. Lymph nodes were harvested either visually or by palpation by dissection along the major venous drainage pathway by the same pathologist. Information on the number of lymph nodes harvested was extracted from pathology reports. Only patients with five or more lymph nodes harvested and analyzed from the surgical specimen were included in the study. The Kaplan–Meier method was used to analyze survival, based on groups of serially ascending values of lymph nodes harvested. Regression analysis was performed with Cox proportional hazards ratio models with right-censored colorectal survival data. The effect of nodal harvest on survival was adjusted for age, sex, preoperative carcinoembryonic antigen (CEA) level, neoadjuvant chemoradiation (NCRT), pathological tumor stage, histological type, differentiation, margin positivity, angioinvasion, perineural invasion, and lymphovascular infiltration (LVI). Stepwise selection method was used to identify the significant determinants of survival. The Mann–Whitney *U* test was used to compare the median number of lymph nodes harvested from specimens. Statistical analysis was performed with the SAS/STAT statistical software (SAS system, version 9.0; SAS Institute, Cary, NC).

Results

Of 131 patients, 61 had stage II cancer and 70 had stage III cancer. Fifty-six percent of patients were male. There were 55 colon cancers and 76 rectal cancers in the sample. Mean follow up for the population was 4.1 years (SD, 3.4). When survival was analyzed based on groups of serially ascending values of harvested lymph nodes, the most significant survival benefit was seen in those who had 14 or more nodes harvested in both colon and rectal cancers (Table 1). The same advantage was observed for the total population of stages II and III CRCs (Fig. 1). When stages II and III cancers were taken separately, a similar maximal survival benefit was seen when more than 14 nodes were available for analysis (stage II, $p=0.07$; stage III, $p=0.03$) (Figs. 2 and 3). Those with a harvest of more than 14 lymph nodes showed lower risk of death with a hazard ratio of 0.37 (95 % CI, 0.18–0.77; $p=0.007$) in a simple linear regression model. In an initial multivariable analysis, advanced age, male sex, LVI, and preoperative CEA levels were found to be other factors significantly associated with survival other than the lymph node harvest (Table 2). Using multiple regression analysis with stepwise selection, the lymph node harvest remained significant with a hazard ratio of 0.19 (95 % CI, 0.066–0.593; $p=0.004$) after adjusting for the abovementioned factors under the final model confirming the lymph node effect (Table 3). Median number of lymph nodes harvested in those who had NCRT was significantly lower (NCRT, 8; range, 5–20 vs. no NCRT, 11; range, 5–45; $p=0.0128$) (Table 4). Twenty-nine percent ($n=18$) of stage II cancers and 31 % ($n=22$) of stage III cancers

Table 1 Comparison of overall survival in colon and rectal cancers based on ascending values of lymph nodes harvested

Lymph node groups	Rectal cancer; mean survival (SE) in years	*p*-value	Colon cancer; mean survival (SE) in years	*p*-value
<6 vs. ≥6	4.0 (1.38) and 3.4 (0.28)	0.759	1.9 (0.35) and 6.5 (0.44)	0.356
<7 vs. ≥7	3.7 (0.77) and 3.4 (0.30)	0.729	1.4 (0.53) and 6.6 (0.44)	0.125
<8 vs. ≥8	3.2 (0.56) and 3.6 (0.32)	0.445	1.6 (0.33) and 6.5 (0.48)	0.580
<9 vs. ≥9	3.6 (0.48) and 3.5 (0.35)	0.988	1.6 (0.22) and 6.6 (0.47)	0.505
<10 vs. ≥10	3.4 (0.44) and 3.6 (0.37)	0.628	2.2 (0.27) and 6.9 (0.46)	0.103
<11 vs. ≥11	3.3 (0.40) and 3.8 (0.39)	0.295	2.3 (0.22) and 6.8 (0.51)	0.426
<12 vs. ≥12	3.1 (0.36) and 4.3 (0.43)	0.050	3.8 (0.43) and 7.2 (0.42)	0.091
<13 vs. ≥13	3.2 (0.35) and 3.7 (0.36)	0.033	4.0 (0.35) and 7.0 (0.60)	0.093
<14 vs. ≥14	3.2 (0.34) and 3.7 (0.38)	0.032	3.9 (0.33) and 7.5 (0.59)	0.085
<15 vs. ≥15	3.4 (0.32) and 3.6 (0.46)	0.230	3.9 (0.33) and 7.5 (0.59)	0.085
<16 vs. ≥16	3.5 (0.31) and 3.6 (0.52)	0.340	4.0 (0.31) and 7.4 (0.67)	0.128
<17 vs. ≥17	3.5 (0.32) and 3.5 (0.52)	0.340	4.1 (0.29) and 7.3 (0.85)	0.331
<18 vs. ≥18	3.6 (0.77) and 3.3 (0.30)	0.344	4.2 (0.26) and 6.9 (1.30)	0.856

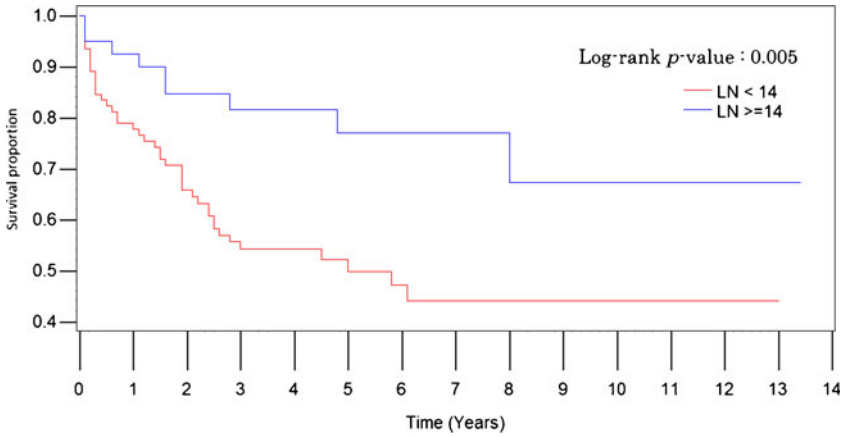

Fig. 1 Overall survival for stages II and III CRC based on the number of lymph nodes harvested

had more than 14 nodes analyzed in this population. The median lymph node harvest was 10 (range, 5–26) for stage II and 11 (range, 5–45) for stage III (p=0.39).

Discussion

Several authors have suggested differing numbers of optimal nodal analysis for accurate staging in CRC [17–20]. In the current study, a significant survival benefit is starting to emerge at the 12 node marks, although the maximum benefit is observed with 14 or more nodes (Table 1). When survival of patients with less than 14 nodes harvested was compared with those with a higher number (eg. <14 nodes vs. ≥15, ≥16, ≥17, ≥18), the significance of survival benefit remained with higher nodal harvest too. The number of nodes analyzed has been shown to affect survival in both node-positive and -negative patients. Rivedulla-Serrano et al. observed the highest 5-year survival rate in node-negative disease with more than 14 nodes harvested [21]. The current study also observed a similar benefit in overall survival for node-negative (stage II) disease with 14 or more nodes harvested for analysis. This may be attributed to a low false-negative rate during staging, with an increased nodal harvest. In a recent study, Peeples et al. reported 24 and 36 nodes, respectively, for stages II and III cancers as being a significant number affecting survival [22]. This number is significantly higher than that recommended by the ACP and NCCN. The authors feel that recommending two values for two stages, that is, stage II and stage III, and a lesser number of nodes for node-negative disease questions the practical implication of such recommendations. A statistically significant hazard ratio of 0.37 indicates a reduced risk of overall mortality when 14 or more nodes were analyzed in this population. In the current study population, long course NCRT was administered for locally advanced rectal tumors based on computer tomographic scan evidence. Though NCRT had no significant effect on survival in this population (Table 2), we and others have observed that it reduces the median lymph node harvest in rectal cancer [23, 24]. The median number of lymph nodes harvested from those who had NCRT was significantly lower in this population (Table 4). However, the survival benefit of nodal harvest remained significant when adjusted for the effect of NCRT under a multifactorial analysis. In the final

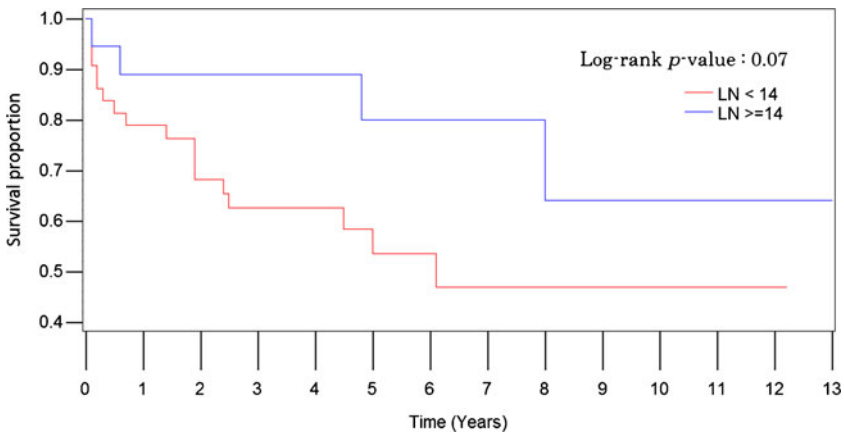

Fig. 2 Overall survival for stage II CRC based on the number of lymph nodes harvested

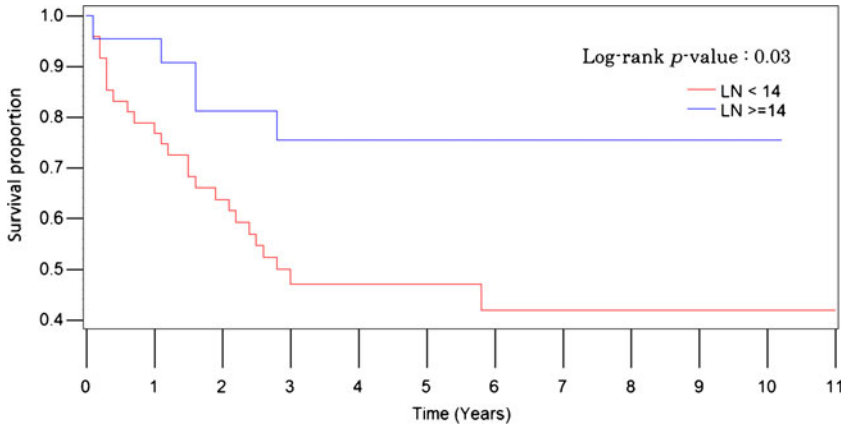

Fig. 3 Overall survival for stage III CRC based on the number of lymph nodes harvested

model with stepwise analysis, NCRT was not shown to be a significant determinant of survival in this population (Table 3), although this could be attributed to the low numbers. A median node harvest of 10 for stage II and 11 for stage III cancers in the current study is higher than a median of 9 as reported by large community-based studies from the USA [15]. Specimens with more than five nodes were selected for the study to eliminate a bias in the statistical process. The lowest number of recommended nodes in literature is six nodes. The distribution of the nodal harvest is expected to be skewed as the study involved cancers with more than five nodes harvested. LVI of tumor was observed to be an independent significant risk factor in this population. Evidence is emerging to suggest that LVI could indicate the likelihood of nodal metastasis in large bowel cancer [25]. This needs to be evaluated further as LVI could be used as an indicator to consider the use of additional techniques to increase nodal harvest or improve detection of metastasis in such specimens. In the absence of such technology, the possibility of LVI as an indicator for adjuvant therapy in node-negative disease should be considered. The number of nodes harvested for examination will depend on the extent and technique of surgical dissection, patients' anatomical factors, and the pathologist dissecting the specimen. This study includes operations performed by the same surgical team and specimens reported by the same pathologist. Porter et al. from Ontario reported a nodal harvesting of above 12 nodes in only 22 % of the cancers from a local population and an increase of up to 31 % through audit feedback over a 5-year period [26]. The current study reports a nodal harvesting of greater than 14 in 29 % of stage II and 31 % of stage III cancers, respectively, which is comparable to above figures.

In conclusion, our data indicate that a lymph node harvest of 14 or more nodes will result in a significant better survival in both node-positive and node-negative disease. Hence, this study provides evidence that nodal harvest has a significant survival benefit in CRC. Staging of the disease could be more accurate with increased nodal harvesting. Histological evidence of lymphovascular invasion may indicate a possibility of nodal metastasis, a feature which may be a useful indicator

Table 2 Initial multivariable analysis using Cox proportional hazard model for identified survival determinants

Variable	Hazard ratio	95 % CI	*p*-value
Lymph node harvest	0.187	0.044–0.782	0.021[a]
Age	1.064	1.021–1.110	0.003[a]
Sex	3.108	1.225–7.883	0.017[a]
Site (colon vs. rectum)	1.607	0.458–5.633	0.458
Histology	1.840	0.394–8.595	0.438
Differentiation	1.241	0.695–2.215	0.466
pT stage	0.947	0.419–2.139	0.896
LVI	19.581	1.789–214.547	0.015[a]
PNI	0.599	0.063–5.678	0.655
AI	0.247	0.031–1.951	0.185
Margin positivity	0.745	0.172–3.225	0.693
Preoperative CEA	1.001	1.000–1.002	0.096
Neoadjuvant CRT	2.175	0.442–10.704	0.339

PT pathological tumor, *LVI* lymphovascular invasion, *PNI* perineural invasion, *AI* angioinvasion, *CEA* carcinoembryonic antigen, *CRT* chemoradiation therapy

[a] Significant values

Table 3 Effect of lymph node harvest in stages II and III CRC cancers adjusted for other determinants in the final model using multiple regression analysis with stepwise selection

Variable	Hazard ratio	95 % CI	*p*-value
Lymph node harvest	0.197	0.066–0.593	0.004
Age	1.055	1.020–1.091	0.002
Sex	3.154	1.389–7.159	0.006
LVI	6.791	2.015–22.883	0.002
CEA	1.001	1.000–1.002	0.027

LVI lymphovascular invasion, *PNI* perineural invasion, *AI* angioinvasion, *CEA* carcinoembryonic antigen

Table 4 Effect of neoadjuvant chemoradiation on the nodal harvest

	No NCRT	NCRT	
LN<14 (*n*)	73	18	Total=91
LN>14 (*n*)	38	02	Total=40
Median nodal harvest (range)	11 (5–45)	8 (5–20)	$p=0.0128$

NCRT neoadjuvant chemoradiation

for adjuvant therapy in stage II disease. Combined efforts of the surgeon and the pathologist to increase the nodal harvest from CRC specimens are recommended to improve survival outcome in stages II and III CRC.

Conflict of interest None of the authors have conflicts of interest to be declared.

References

1. Grothy A. Risk assessment in stage II colon cancer: to treat or not to treat. Oncology (Williston Park). 2010;24 Suppl 1:1–2.
2. O'Connell M, Maillard JA, Kahn MJ, et al. Controlled trial of fluorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer. J Clin Oncol. 1997;15:246–50.
3. O'Connell M, Laurie JA, Kahn MJ, et al. Prospectively randomized trial of postoperative adjuvant chemotherapy in patients with high-risk colon cancer. J Clin Oncol. 1998;16:295–300.
4. Benson AB III, Schrag D, Somerfield MR, et al. American society of clinical oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol. 2004;22:3408–19.
5. 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;124:979–94.
6. Engstrom PF, Benson AB III, Saltz L. National comprehensive cancer network: colon cancer. Clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2003;1:40–53.
7. Obrocea FL, Sajin M, Marinescu EC, Stoica D. Colorectal cancer and the 7th revision of the TNM staging system: review of changes and suggestions for uniform pathologic reporting. Rom J Morphol Embryol. 2011;52:537–44.
8. Pheby DF, Levine DF, Pitcher RW, Shepherd NA. Lymph node harvests directly influence the staging of colorectal cancer: evidence from a regional audit. J Clin Pathol. 2004;57:43–7.
9. Ratto C, Sofo L, Ippoliti M, et al. Accurate lymph-node detection in colorectal specimens resected for cancer is of prognostic significance. Dis Colon Rectum. 1999;42:143–54.
10. Vather R, Sammour T, Kahokehr A, Connolly AB, Hill AG. Lymph node evaluation and long-term survival in stage II and stage III colon cancer: a national study. Ann Surg Oncol. 2009;16:585–93.
11. Berberoglu M. Prognostic significance of total lymph node number in patients with T1-4N0M0 colorectal cancer. Hepatogastroenterology. 2004;51:1689–93.
12. Chen SL, Bilchik AJ. More extensive nodal dissection improves survival for stages I to III of colon cancer: a population-based study. Ann Surg. 2006;244:602–10.
13. The Commission on Cancer (CoC) of the American College of Surgeons. Colon Cancer Measures submitted by the CoC to the National Quality Forum (NQF) and endorsed by the NQF in April 2007. *In*: American College of Surgeons. Cancer Program. Available via http://www.facs.org/cancer/qualitymeasures.html. Accessed May 2013.
14. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Colon Cancer Version 3.2013. 2013;National Comprehensive Cancer Network. Available via http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site. Accessed 15 May 2013.
15. 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;97:219–25.
16. Johnson PM, Malatjalian D, Porter GA. Adequacy of nodal harvest incolorectal cancer: a consecutive cohort study. J Gastrointest Surg. 2002;6:883–8.
17. Goldstein NS. Lymph node recoveries from 2427 pT3 colorectal specimens spanning 45 years. Recommendations for a minimum number of recovered lymph nodes based on predictive probabilities. Am J Surg Pathol. 2002;26:179–89.
18. Leibl S, Tsybrovskyy O, Denk H. How many lymph nodes are necessary to stage early and advanced adenocarcinoma of the sigmoid colon and upper rectum? Virchows Arch. 2003;443:133–8.
19. Luna-Pérez P, Rodríguez-Ramírez S, Alvarado I, et al. Prognostic significance of retrieval lymph nodes per specimen in resected rectal adenocarcinoma after chemoradiation therapy. Arch Med Res. 2003;34:281–6.
20. Berberoglu U. Prognostic significance of total lymph node number in patients with T1-4 N0 M0 colorectal cancer. Hepatogastroenterology. 2004;51:1689–93.
21. Rivadulla-Serrano MI, Martínez-Ramos D, Armengol-Carrasco M, et al. Impact of the total number of harvested lymph nodes after colon cancer resections on survival in patients without involved lymph node. Rev Esp Enferm Dig. 2010;102:296–301.
22. Peeples C, Shellnut J, Wasvary H, Riggs T, Sacksner J. Predictive factors affecting survival in stage II colorectal cancer: is lymph node harvesting relevant? Dis Colon Rectum. 2010;53:1517–23.
23. Wijesuriya SRE, Deen KI, Hewavisenthi J, Balawardana J, Perera M. Neoadjuvant therapy for rectal cancer down-stages the tumor but reduces lymph node harvest significantly. Surg Today. 2005;35:442–5.
24. Klos CL, Bordeianou LG, Sylla P, Chang Y, Berger DL. The prognostic value of lymph node ratio after neoadjuvant chemoradiation and rectal cancer surgery. Dis Colon Rectum. 2011;54:171–5.
25. Barresi V, Reggiani Bonetti L, Vitarelli E, Di Gregorio C, Ponz de Leon M, Barresi G. Immunohistochemical assessment of lymphovascular invasion in stage I colorectal carcinoma: prognostic relevance and correlation with nodal micrometastases. Am J Surg Pathol. 2012;36:66–72.
26. Porter GA, Urquhart R, Bu J, Johnson P, Grunfeld E. The impact of audit and feedback on nodal harvest in colorectal cancer. BMC Cancer. 2011;11:2.