ORIGINAL ARTICLE

Effect of Lymph Node Retrieval and Ratio on the Long-Term Survival and Recurrence of Colon Cancer

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Abstract

Objective: To evaluate the association of lymph node retrieval and ratio with the prognosis of colon cancer.
Study Design: A cohort study.
Place and Duration of Study: Ninewells Hospital and Medical School, Dundee, UK, from October 2014 to March 2015.
Methodology: Data was collected for adult patients who were diagnosed with primary adenocarcinoma of colon between 2003 and 2008. The follow-up period was 5-year. The data was collected from regional electronic colorectal cancer database. Kaplan-Meier graph was used to calculate and depict overall survival in different groups of patients.
Results: There were a total of 370 patients with colon cancer. For Dukes stages A and B, there was no significant difference in median overall survival for patients with lymph node retrieval (< 12 nodes vs. > 12 nodes). For Dukes stage C (n=147), median survival for patients with lymph node retrieval < 12 nodes was 4 years vs. 4 years for patients with lymph node retrieval > 12 nodes (p = 0.85). Median survival for patients with lymph node ratio (LNR) < 0.125 was 4 years (range 1 - 11) vs. 3 years (range 0 - 11) for patients with LNR > 0.125 (p = 0.14). There was no significant difference in the recurrence rate based on lymph node retrieval (p = 0.87) and LNR (p = 0.97).
Conclusion: Lymph node retrieval > 12 and reduced LNR < 0.125 had no significant effect on long-term survival and recurrence of colon cancer.

Key Words: *Colonic neoplasm. Lymph node excision. Recurrence. Survival.*

INTRODUCTION

There is conflicting evidence on the association of total number of lymph nodes retrieved and lymph node ratio (LNR) with the prognosis of colon cancer.[1,2] Current clinical guidelines recommended a minimum of 12 lymph nodes to be harvested with the tumour.[3,4] However, huge variation exists among different hospitals in the number of lymph nodes resected.[5] Similarly, there are no international recommendations on the minimum threshold of lymph node ratio to be achieved with tumour resection.[6]

In this study, the aim was to evaluate any association between number of lymph nodes retrieved and prognosis of colon cancer, and whether achievement of any threshold lymph node ratio provides prognostic benefit in colon cancer patients or not.

METHODOLOGY

The study was conducted at Ninewells Hospital and Medical School, Dundee UK, from October 2014 to March 2015. The data was collected for patients who were diagnosed with colon cancer between 2003 and 2008. All the adult patients over the age of 18 years, undergoing complete surgical resection for primary adenocarcinoma of colon, were included in the study. Patients with colon cancer Dukes stage D and rectal cancer were excluded from the study.

The data was collected from electronic colorectal cancer database, which included all the information about patient demographics, pathology of disease, operative procedure, number of lymph nodes, outpatient clinic outcomes, and investigative reports. The electronic clinic letters and radiology reports were reviewed to assess patient's long-term disease recurrence status and 5-year survival. The follow-up period for the study was 5 years. All the patients who had either elective or emergency operation were included in the study that resulted in complete resection of the tumour. The information on disease stage and number of lymph node yield was obtained from pathology reports. Lymph node ratio was calculated by dividing the number of lymph nodes with metastatic disease by total number of lymph node yield of the pathological specimen.

SPSS version 22.0 was used to conduct the data analysis. Mean values with standard deviation and frequencies were obtained for patients in study population and subgroups of Dukes stage of colon cancer for tumour size. Age was calculated in mean with standard deviation. Shapiro-Wilk test was conducted to check for normal distribution of dependent variables that is overall survival, number of lymph node retrieved, and lymph node ratio (p < 0.001). It showed that the data was non-parametric; Mann-Whitney U test was used for

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comparison of overall survival between the groups. The comparison of recurrence rate as a categorical variable between groups was evaluated by chi-square test. Comparison was considered significant if the p-value was less than 0.05. Kaplan-Meier graph was used to calculate and depict overall survival in different groups of patients.

RESULTS

There were a total of 370 patients with colon cancer, of which 181 were males and 189 were females. Mean age of the patients was 72.04 ±10.92 years and mean size of the tumour was 44.89 ±21.41 mm. Mean number of lymph nodes retrieved was 20.06 ±8.63 and mean overall survival rate was 5.33 ±1.92 years.

Median overall survival for patients with less than 12 lymph nodes retrieved (n=63/371, 16.98%) was 4 years ranging from 0 - 11 years; as compared to 5 years, ranging from 0 - 12 years, for patients with more than 12 lymph nodes retrieved (n=308/371, 83.02%). However, there was no significant difference between the groups (p = 0.62). Overall recurrence rate was 9.16% (n=34/371), of which 7.01% (n=26/371) had local recurrence. The patient characteristics for Dukes stage A, B and C colon cancer is summarised in Table I.

Table I: Summary of patient and pathological characteristics.

Dukes Stage	A	B	C
Total number (n)	50	174	147
Mean age	70.37 (SD 11.23)	72.95 (SD 9.90)	71.56 (SD 10.14)
Mean tumour size (mm)	31.05 (SD 21.84)	46.91 (SD 19.56)	47.73 (SD 21.71)
Mean number of lymph node	16.86 (SD 6.63)	20.75 (SD 8.67)	20.42 (SD 8.99)
Local recurrence rate (%)	0%	3.44% (n=6/174)	13.60% (n=20/147)
Distant recurrence (%)	0%	3.44% (n=6/174)	1.36% (n=2/147)
Mean overall survival (years ±SD)	5.58 ±2.85	5.76 ±2.73	4.67 ±4.37

There were a total of 50 patients (13.4%) with Dukes stage A colon cancer. Median overall survival for patients with lymph node retrieval of less than 12 lymph nodes (n=14/50, 28%) was 4 years, ranging from 1 - 11 years as compared to 5 years ranging from 1 - 10 years, for patients with lymph node retrieval of more than 12 nodes (n=36/50, 72%). However, there was no significant difference between the groups (p = 0.56). There were no cases of recurrence.

There were a total of 174 patients with Dukes stage B colon cancer. Median overall survival for patients with lymph node retrieval of less than 12 nodes (n=27/174, 15.55%) was 5 years ranging from 1 - 9 years as compared to 6 years ranging from 0 - 12 years, for patients with lymph node retrieval of more than 12 nodes (n=147/174, 84.48%). However, there was no significant difference between the groups (p = 0.31). There were 12 out of 174 cases (6.89%) that had recurrence, of which 11 cases (91.67%) had more than 12 lymph nodes retrieved and only one case had less than 12 lymph nodes removed (p = 0.78). There were a total of 6 (3.44%) cases of distant metastasis to liver and 6 (3.44%) cases of local metastases.

There were a total of 147 patients with Dukes stage C colon cancer. Median overall survival for patients with lymph node retrieval of less than 12 nodes (n=22/147, 14.96%) was 4 years, ranging from 0 - 11 years, as compared to 4 years also ranging from 0 - 11 years, for patients with lymph node retrieval of more than 12 nodes (n=125/147, 85.03%). However, there was no significant difference between the groups (p = 0.85, Figure 1).

Median overall survival for patients with lymph node ratio (LNR) of less than 0.125 (n=66/147, 44.89%) was 4 years, ranging from 1-11 years, as compared to 3 years, ranging from 0-11 years, for patients with LNR of more than 0.125 (n=81/147, 55.10%). However, there was no significant difference between the groups (p = 0.14, Figure 2).

There were 22 out of 147 cases (14.9%) with recurrence in this group; 20 cases of local recurrence and 2 cases of distant metastases to liver. Only two of the 22 cases

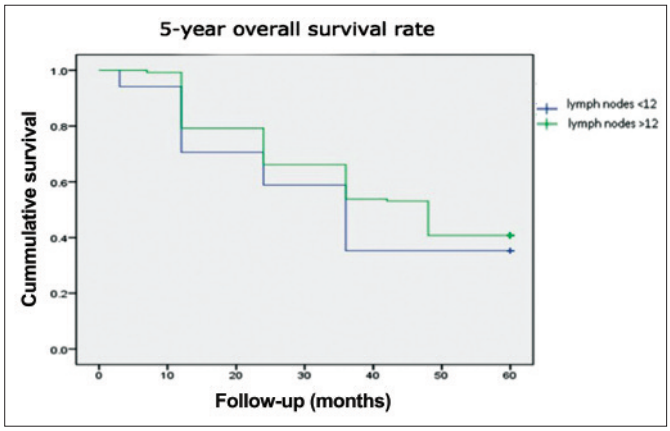

Figure 1: 5-year overall survival of patients with Dukes stage C colon cancer: comparison based on lymph node retrieval (P = 0.40).

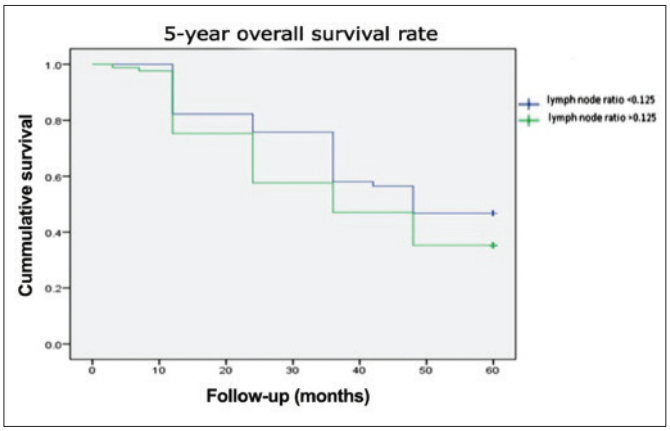

Figure 2: 5-year overall survival of patients with Dukes stage C colon cancer: comparison based on lymph node ratio (P = 0.11).

(9.1%) had lymph node retrieval of less than 12, while 20 cases (90.9%) had lymph node retrieval of more than 12 with no significant difference (p = 0.87). Similarly, there were 13 cases (64%) with LNR > 0.125, while 9 cases (36%) had LNR < 0.125 with no significant difference between the groups (p = 0.97).

DISCUSSION

Overall, the study has shown that there was no significant association between total number of lymph nodes retrieved and overall survival and recurrence of the patients for colon cancer Dukes stage A, B and C. Similarly, lymph node ratio had no significant prognostic implication on the overall survival and recurrence of patients with colon cancer.

The recommendation of minimum 12 lymph nodes removal was suggested in 1990 Working Party Report to the World Congress of Gastroenterology and the message was reinforced by National Cancer Institute-sponsored panel of experts.[4] This evidence was based on five retrospective studies and one randomised controlled trial. The outcome of retrospective studies was conflicting, with studies favouring extended lymphadenectomy mainly in Dukes stage C disease.[4] Similarly, beneficial effect of more extensive lymphadenectomy was only seen in advanced left-sided colon cancer as reported by previous RCT.[7]

National Centre Institute's Surveillance, Epidemiology and End Results program was conducted on 116,995 patients in the USA to determine the proportion of colorectal cancer patients who received adequate lymph nodes resection. It showed that most of the patients with colorectal cancer had less than 12 nodes removed.[2] On the other hand, single centre studies had demonstrated higher proportion of colon cancer patients with more than 12 lymph nodes resection, in particular those centres that used standard method of pathological examination for lymph node evaluation.[5] Similarly, our single centre study also demonstrated higher lymph node yield with the mean lymph node retrieval of 20.04.

There was no significant difference in the overall outcome of patients in this data, based on the number of lymph nodes removed. This finding was consistent in all stages of colon cancer, particularly, in the subgroup of patients with local recurrence. There were a total of 34 cases of recurrence, of which 26 were locally recurred. Majority of these cases (n=25/26) had more than 12 lymph nodes harvested. Of the 12 cases of Dukes B colon cancer that had recurrence, 6 cases locally recurred. All these cases had more than 12 lymph nodes retrieved.

A previous study showed no significant improvement in 5-year survival for colon cancer patients at hospitals with higher lymph node evaluation compared to hospitals with lower lymph node retrieval.[8] The rate of minimum number of 12 lymph nodes removal varied from 16% to 61% among different hospitals. Similarly, in this study, number of lymph nodes retrieval did not make any significant difference to long-term survival and recurrence Dukes C colon cancer patients. Majority of the Dukes C stage cancer patients (n=21/22) with recurrence had more than 12 lymph nodes retrieved.

Retrieval of lymph nodes in colon cancer depended on multiple factors. Previous studies have shown that lymph node recovery was dependent on the location and anatomy of tumour.[9] The lymph node retrieval was significantly increased in patients of age less than 65, sigmoid and right sided tumour, and small tumour size.[10,11] Surgical skill was also an important factor in adequate lymph node recovery.[10] An appropriate surgical technique involved resection of tumour along mesocolon, ligation of feeding artery at its origin and removal of macroscopic metastatic lymph node disease along with apical node at the base of feeding artery.[9]

Retrieval of lymph nodes and identification of positive lymph nodes were shown to be significantly affected by pathologists' lymph node examination.[12] The College of American Pathologists published guidelines and recommended pathologists to use additional visually enhancing techniques to appraise lymph node specimen, if fewer than 12 lymph nodes were retrieved.[13] Fat clearance from the pathological sample had been shown to produce significant higher yield of lymph nodes.[12] However, if national guidelines mandate minimum harvest of 12 nodes in each sample, it can discourage pathologists to look for additional positive lymph nodes once minimum of 12 lymph nodes are identified.[13]

A recent systematic review confirmed independent prognostic impact of lymph node ratio in colorectal cancers, based on the data from 16 studies including 131,953 patients.[14] However, the review included studies evaluating both stage III colon and rectal tumours, patients who underwent oncological treatment, data from observational studies, variable categories of LNR, and differences in co-morbidities in comparison groups. Our data, on the contrary, did not show any significant difference in the long-term outcome of patients with Dukes stage C colon cancer based on the lymph node ratio. Although, nearly half of the recurrent cases (n=10/22) in Dukes stage C cancer patients had lymph node ratio of less than 0.125, but it did not have any beneficial effect on the mean overall long-term recurrence compared to those with lymph node ratio of more than 0.125.

Different studies have used different cut-off values to categorise and compare lymph node ratios.[10,15] Vather *et al*. compared lowest decile (0.0-0.1) to highest decile (0.9-1.0) for ratio; while in other studies, lymph node ratio groups were divided into quartiles showing

significant difference between them.[15] At the authors' centre, the mean yield of lymph node was high (20.06); hence, an overall reduction in the lymph node ratio for all cases. There were very few patients with lymph node ratio of more than 0.25. The authors used the cut-off value for lymph node ratio to be 0.125 to have substantive number of patients in both comparable groups. Using a higher value would have led to statistical error for comparison between groups.

This study had certain limitations. In this retrospective data, the cohort groups were non-randomised and not matched. The association of other co-variates with long-term outcome of colon cancer such as patient characteristics, co-morbidities, tumour location and size, neurovascular invasion, degree of differentiation, type of surgery (laparoscopic and open approach), nature of the surgery (elective versus emergency), and the sub-specialisation of the surgeons were not evaluated.

There are a lot of other factors that can affect lymph node yield. As recommended in the guidelines for the management of colorectal cancer, adequate resection of lymph nodes at origin of feeding vessels should be carried out along with any lymph node suspected of being positive outside the field of resection.[4] More emphasis should be paid on surgical skill of lymph node resection and technique of pathological examination.[4]

CONCLUSION

Lymph node retrieval and ratio on the long-term prognosis of colon cancer had no significant effect on the long-term survival outcome and recurrence.

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