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ORIGINAL ARTICLE

Prognostic significance of the metastatic lymph node ratio for survival in colon cancer

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Summary

Purpose: *The metastatic lymph node ratio (LNR) is defined as the number of metastatic lymph nodes divided by the total number of lymph nodes removed. The aim of this study was to investigate the prognostic significance of the metastatic LNR in patients with colon cancer.*

Methods: *One-hundred twenty-five patients with stage III colon cancer admitted to the Istanbul University Oncology Institute between 1995 and 2005 were retrospectively evaluated. The median LNR was 0.2, and this figure was accepted as cut-off value in the present study. Overall survival (OS) and disease-free survival (DFS) were calculated using the Kaplan-Meier method. Log-rank test was used for intergroup comparisons. The significance level was put at p<0.05.*

Results: *Of the 125 patients, 58 (46.4%) were males and 67 (53.6%) females with median age 57 years. The mean OS in patients with a LNR <0.2 was 120.5±7.3 months, with a LNR ≥0.2 was 92.8±9.0 months Although clinically significant, the difference between the groups was statistically insignificant (p=0.074). The mean duration of DFS in patients with a LNR <0.2 was 100.6±8.6 months and for those with a LNR ≥0.2 it was 71.7±8.3 months (p=0.017). The 5-year DFS rate in patients with a LNR ≥0.2 was 42.3%; it was 64.1% in those with LNR<0.2. The difference between the groups was statistically significant (p=0.017).*

Conclusion: *The determination of the optimal cut-off value for the LNR in future prospective studies will help defining prognosis with better accuracy in colon cancer patients.*

Key words: colon cancer, metastatic lymph node ratio, prognostic significance, survival

Introduction

Colon cancer is one of the leading causes of cancer-related mortality in the world, Turkey included. This malignancy is thought to be more prevalent in developed countries due to dietary habits [1]. In the US, colon cancer, together with rectal cancer, is the 2nd leading cause of cancer-related deaths, constituting approximately 10% of all cancer-related deaths. In Turkey, colon and rectal cancers are the 8th and 9th leading cancers in males, respectively, and the 6th and 10th leading cancers in females, respectively.

Many prognostic factors for colorectal cancer have been studied [2,3]. The pathologic stage is the most important factor determining the prognosis after curative resection. Invasion of the lymph nodes and increase in the tumor (T) size significantly reduce the 5-year OS and DFS [4].

It is widely accepted that nodal involvement is a crucial factor in localized tumors of the colon and rectum [5]. Additionally, the number of lymph nodes involved has been shown to affect prognosis in colorectal cancer.

The increased number of lymph nodes removed has been found to be associated with increased survival [6]. The major contribution of extended lymph node dissection is accurate staging rather than the potential therapeutic benefit [7,8].

Recently, the LNR has been considered as a strong prognostic factor for colon cancer [9]. Similarly, a higher LNR has been considered to be a prognostic indicator for poor survival in patients with gastric and pancreatic cancers [10].

It is well-known that adjuvant chemotherapy is beneficial on survival in patients with stage III colon cancer.

In the present study, 125 patients with stage III co-

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lon cancer were retrospectively evaluated to determine the prognostic value of the metastatic LNR.

Methods

The medical records of 125 patients who were admitted at the Istanbul University Oncology Institute between 1995 and 2005 and diagnosed with stage III colon cancer according to TNM staging system were retrospectively evaluated.

Analysed were gender, histological cancer type, grade, stage, tumor location, surgical margin status, ECOG performance status, lymph node invasion and presence of capsular invasion.

The median LNR was calculated at 0.2, and this figure was accepted as cut-off value in the present study.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences v. 11.0 program (SPSS Inc., Chicago, IL, USA). OS and DFS were calculated using the Kaplan-Meier method. Log-rank test was used for intergroup comparisons. The statistical significance was put at $p<0.05$.

Results

The mean and median patient age were 56.26± 13.89 and 57 years (range 24-84), respectively (Figure 1). There were 58 (46.4%) male and 67 (53.6%) female patients. The median duration of follow-up was 42 months (range 7-149) and the mean duration 48.63±33.98 months. Location of the tumors is shown in Table 1. The surgical margin status of the patients is shown in Table 2. The patient performance status (PS) is depicted in Table 3. TN staging is shown in Table 4. Distribution of patients according to pathological grades is presented in Table 5, with grade II predominating almost completely (n=97; 77.6%). Presence of capsular invasion is shown in Table 6. Table 7 shows the distribution of patients according the total number of lymph nodes removed and Table 8 shows

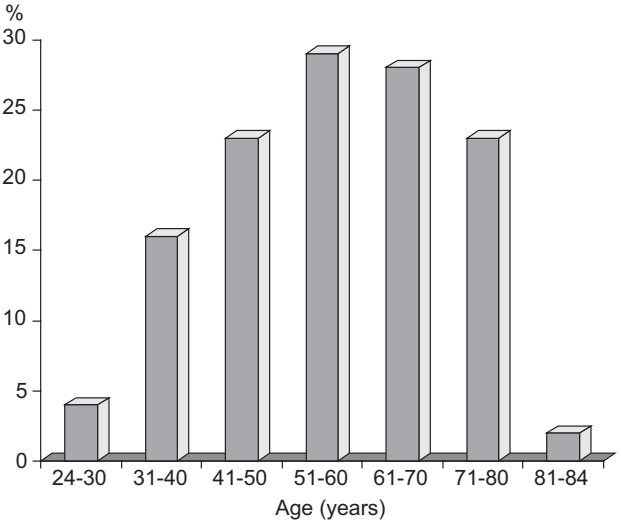

Figure 1. Patient distribution according to age groups.

Table 1. Location of the tumors

Location	*Patients, n (%)*
Cecum	15 (12)
Ascending colon	4 (3.2)
Hepatic flexure	6 (4.8)
Right colon	24 (19.2)
Transverse colon	15 (12)
Splenic flexure	5 (4)
Left colon	12 (9.6)
Descending colon	3 (2.4)
Sigmoid	32 (25.6)
Rectosigmoid	8 (6.4)
Sigmoid and cecum (double primary tumor)	1 (0.8)
Total	125 (100)

Table 2. Surgical margin status

Status	*Patients, n (%)*
Negative	124 (99.2)
Positive	1 (0.8)
Total	125 (100)

Table 3. Patient ECOG performance status

Performance status	*Patients, n (%)*
0	88 (70.4)
1	35 (28)
2	1 (0.8)
3	1 (0.8)
Total	125 (100)

Table 4. Number of patients according to TN stage

Stage	*N_1 Patients, n (%)*	*N_2 Patients, n (%)*	*Total Patients, n (%)*
T_1	0 (0)	0 (0)	0 (0)
T_2	4 (3.2)	0 (0)	4 (3.2)
T_3	58 (46.4)	37 (29.6)	95 (76)
T_4	16 (12.8)	10 (8)	26 (20.8)
Total	78 (62.4)	47 (37.6)	125 (100)

Table 5. Patient distribution according to tumor grade

Grade	*Patients, n (%)*
I	9 (7.2)
II	97 (77.6)
III	5 (4)
IV	14 (11.2)
Total	125 (100)

Table 6. Presence of capsular invasion

Capsular invasion	*Patients, n (%)*
Absent	5 (4)
Present	38 (30.4)
Not specified	82 (65.6)
Total	125 (100)

Table 7. Patient distribution according to the total number of lymph nodes removed

Number of lymph nodes	*Patients, n (%)*
2	3 (2.4)
3	1 (0.8)
4	2 (1.6)
5	1 (0.8)
6	2 (1.6)
7	4 (3.2)
8	5 (4)
9	8 (6.4)
10	5 (4)
11	7 (5.6)
12	5 (4)
13	6 (4.8)
14	7 (5.6)
15	9 (7.2)
16	4 (3.2)
17	2 (1.6)
18	4 (3.2)
19	4 (3.2)
20	7 (5.6)
21	4 (3.2)
22	7 (5.6)
23	3 (2.4)
24	2 (1.6)
25	5 (4)
28	2 (1.6)
30	2 (1.6)
33	3 (2.4)
34	1 (0.8)
36	1 (0.8)
37	2 (1.6)
40	1 (0.8)
41	1 (0.8)
44	1 (0.8)
45	1 (0.8)
46	1 (0.8)
49	1 (0.8)
53	1 (0.8)
57	1 (0.8)
Total	125 (100)

the number of negative lymph nodes. The number of positive lymph nodes removed is shown in Table 9. Ninety-five (76%) patients are alive (Table 10), 71 (56.8%) of them with no evidence of disease.

Overall survival

The mean duration of OS was 109.2±6.3 months (95% confidence interval [CI] 96.9-121.5). The 5-year OS rate was 70.3% (Figure 2).

The 5-year OS rate was 65.4% in patients with capsular invasion; no patient without capsular invasion died (Figure 3).

Overall survival according to gender

In males the mean duration of OS was 85.6±9.1

Table 8. Patient distribution according to the number of negative lymph nodes removed

Number of negative lymph nodes	*Patients, n (%)*
0	2 (1.6)
1	3 (2.4)
2	4 (3.2)
3	4 (3.2)
4	5 (4)
5	5 (4)
6	5 (4)
7	7 (5.6)
8	6 (4.8)
9	7 (5.6)
10	4 (3.2)
11	8 (6.4)
12	5 (4)
13	6 (4.8)
14	9 (7.2)
15	7 (5.6)
16	3 (2.4)
17	4 (3.2)
18	3 (2.4)
19	4 (3.2)
20	1 (0.8)
21	4 (3.2)
22	2 (1.6)
23	1 (0.8)
25	1 (0.8)
26	1 (0.8)
27	1 (0.8)
28	1 (0.8)
33	3 (2.4)
34	2 (1.6)
39	1 (0.8)
42	2 (1.6)
43	1 (0.8)
46	1 (0.8)
52	1 (0.8)
56	1 (0.8)
Total	125 (100)

Table 9. Patient distribution according to the number of positive lymph nodes removed

Number of positive lymph nodes	*Patients, n (%)*
1	41 (32.8)
2	21 (16.8)
3	16 (12.8)
4	12 (9.6)
5	8 (6.4)
6	1 (0.8)
7	3 (2.4)
8	10 (8)
9	4 (3.2)
10	2 (1.6)
11	1 (0.8)
12	1 (0.8)
13	1 (0.8)
14	1 (0.8)
16	1 (0.8)
19	1 (0.8)
27	1 (0.8)
Total	125 (100)

Table 10. Patient outcome

Patient outcome	*Patients, n (%)*
Alive	95 (76)
Dead	30 (24)

months (95% CI 67.7-103.5) and the 5-year OS 52.4%, and in females the corresponding figures were 133.7±5.5 months (95% CI, 123.0-144.4) and 88.3%. The 5-year OS rate of females was significantly longer than that of the males (p<0.001) (Figure 4).

Overall survival according to lymph node ratio

In patients with LNR<0.2 the mean duration of OS was 120.5±7.3 months (95% CI, 106.1-134.9) and the 5-year OS 75.3%.

In patients with LNR≥0.2 the mean duration of OS was 92.8±9.0 months (95% CI, 75.2-110.3) and the 5-year OS 64.0%. Although clinically important, the difference between the groups regarding OS was not statistically significant (p=0.074) (Figure 5).

Disease-free survival

The mean duration of DFS was 87.7±6.3 months (95% CI, 75.4-100.0) and the 5-year DFS 53.1% (Figure 6).

The mean duration of DFS in patients without capsular invasion was 101.8±19.9 months (95% CI, 62.9-

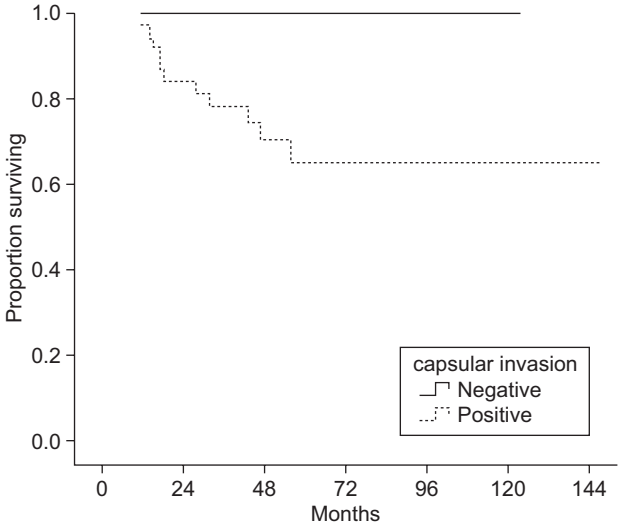

Figure 3. Patient overall survival with/ without capsular invasion.

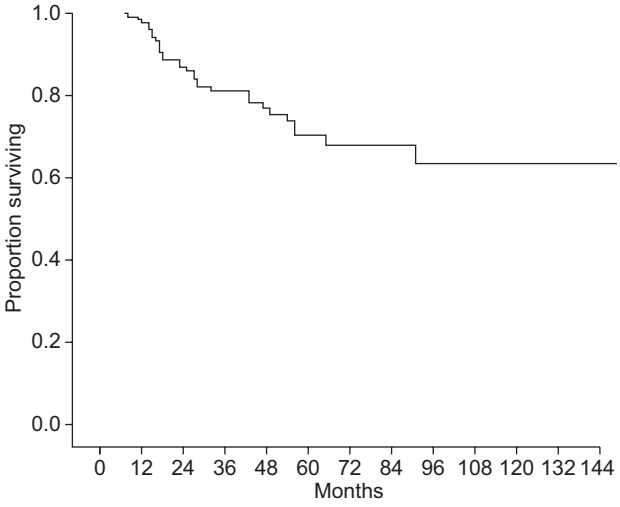

Figure 2. Patient overall survival.

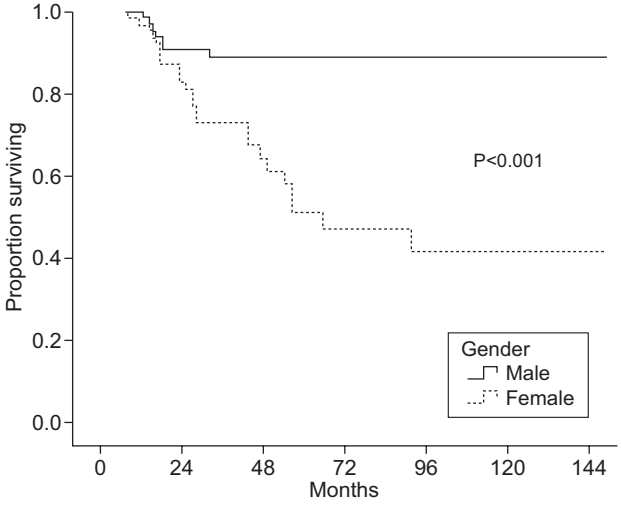

Figure 4. Patient overall survival according to gender.

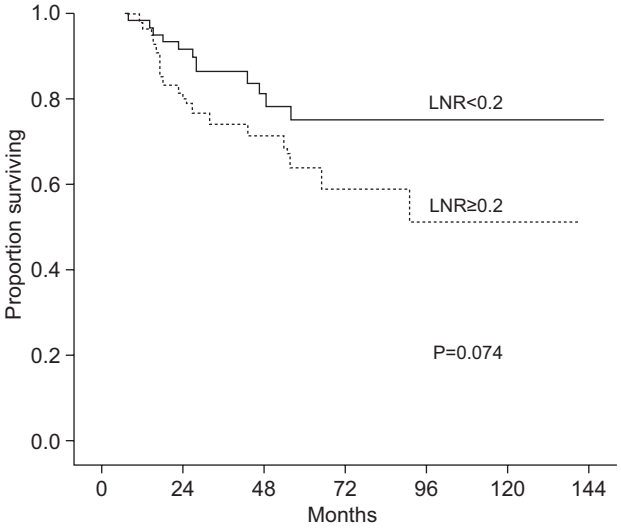

Figure 5. Patient overall survival according to lymph node ratio (LNR).

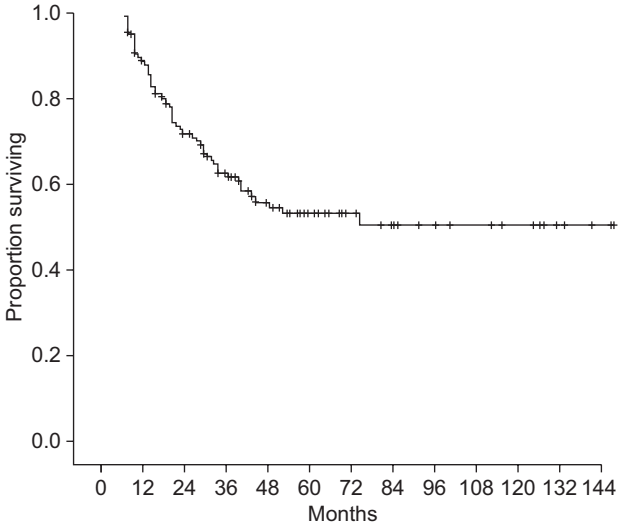

Figure 6. Patient disease-free survival.

140.7). The 5-year DFS rate could not be calculated due to inadequate sample size (Figure 7).

The mean duration of DFS in patients with capsular invasion was 88.1±10.7 months (95% CI, 67.2-109.0) and the 5-year DFS 50.95±8.8 months; the difference for DFS between patients with and without capsular invasion was not statistically significant (p=0.339).

Disease-free survival according to gender

The mean duration of DFS in males was 78.5±9.0 months (95% CI, 61.0-96.1) and the 5-year DFS 43.7% (Figure 8).

The mean duration of DFS in females was 94.4±8.7 months (95% CI, 77.4-111.4) and the 5-year DFS 60.8%. There was no significant difference between genders in terms of 5-year DFS rate (p=0.211).

Disease-free survival according to lymph node ratio

According to the metastatic LNR, the mean duration of DFS in patients with a LNR <0.2 was 100.6±8.6 months (95% CI, 83.7-117.5) and the 5-year DFS 64.1% (Figure 9).

The mean duration of DFS in patients with a LNR ≥0.2 was 71.7±8.3 months (95% CI, 55.4-88.0) and the 5-year DFS 42.3%. The difference between the groups with a LNR <0.2 and ≥0.2 was statistically significant in terms of 5-year DFS (p=0.017).

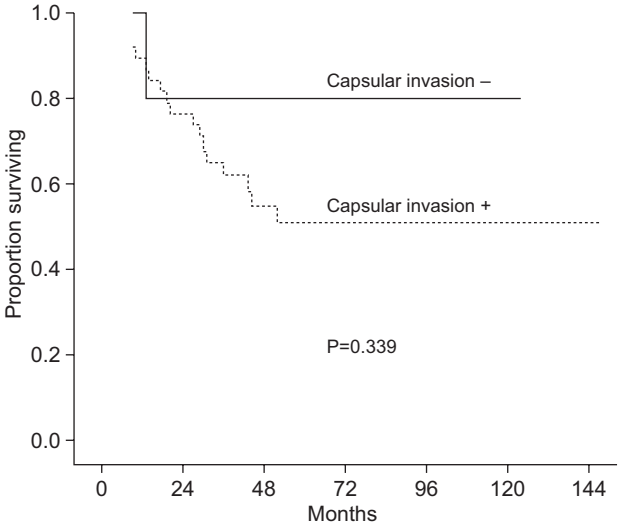

Figure 7. Disease-free survival of patients with/ without capsular invasion.

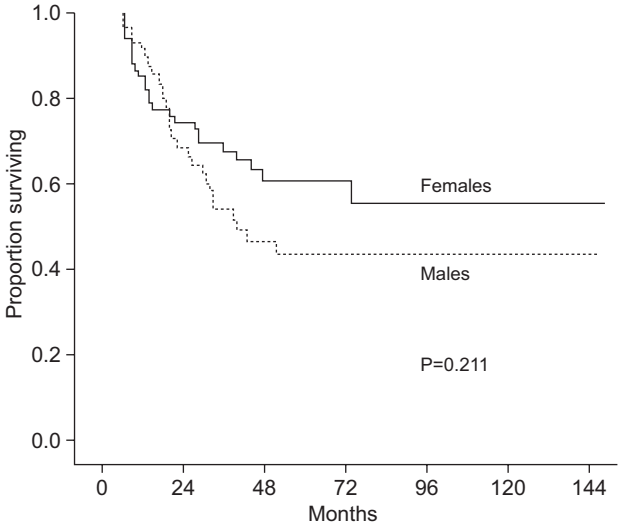

Figure 8. Patient disease-free survival according to gender.

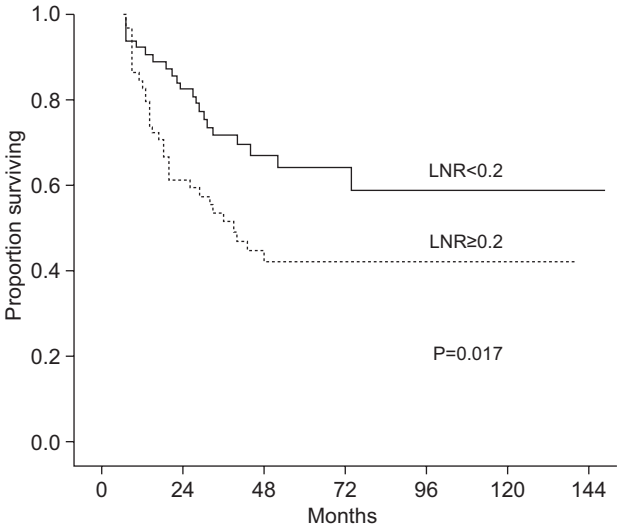

Figure 9. Disease-free survival according to lymph node ratio (LNR).

Discussion

Surgical treatment of colon cancer includes removal of the involved colon segment and the associated lymph nodes. Adjuvant chemotherapy is recommended for high-risk colon cancer patients, including those with lymph node involvement (stage III) and some selected patients (stage II) without lymph node involvement [11-22].

The evaluation of at least 12 lymph nodes has been recommended for adequate staging (54-56). Other studies have reported that the likelihood of accurate staging increases when the number of lymph nodes evaluated for staging is 12-17 [23,24]. It has been reported that the survival rate increases with increasing number of lymph nodes removed [8]. The median number of lymph nodes removed was 18 in the current retrospective study.

The recurrence rate following curative resection is 70% in patients with stage III colon cancer.

Several investigators have evaluated the effects of the metastatic LNR, especially in breast and pancreatic cancers, and found that the metastatic LNR is associated with OS and DFS rates [25,26].

Although the major contribution of extended lymphadenectomy is accurate staging, extended lymphadenectomy may also provide a potential therapeutic benefit in patients with colon cancer. Recently, the positive LNR has been considered to be a strong prognostic indicator in colon cancer [2,5,6,25]. A higher LNR has been demonstrated to be a prognostic indicator for poor survival in gastric and pancreatic cancers [25].

It has also been reported that an increased number of negative lymph nodes is independently associated with improved long-term survival in patients with stage III (IIIB and IIIC) colon cancer [27].

The mortality rate can be reduced by 33% with the use of adjuvant chemotherapy in patients with stage III colon cancer. Six months of fluorouracil + leucovorin treatment was used as standard adjuvant chemotherapy in Turkey until early 2005, when oxaliplatin was approved for use in lymph node-positive colon cancer. Since that time, a fluorouracil + leucovorin + oxaliplatin regimen has been widely used.

The majority of the patients in the current retrospective study received fluorouracil + leucovorin as adjuvant chemotherapy [18,19].

The distribution and the number of involved lymph nodes is an important prognosticator in colon cancer [28].

The LNR is a significant prognostic factor in patients with colon adenocarcinomas. The number of positive lymph nodes, the number of lymph nodes removed, and the LNR have been shown to be significant factors [9].

Schumacher et al. [29] emphasized the significance of the metastatic LNR in predicting survival in patients with colon cancer. In that particular study, the specific analysis of stage III patients revealed that a LNR value of 0.18 was predictive of DFS.

The prognostic significance of the metastatic LNR in stage III colon cancer has been recently emphasized in a Korean study [30].

The TNM system maintained by the American Joint Committee on Cancer (AJCC) is currently being used worldwide. The number of metastatic lymph nodes plays an important role in the TNM staging system. However, N staging is easily affected by the extension of lymph node dissection, surgical technique, and the thoroughness of the pathologist and technique of lymph node isolation. Thus, these variables may lead to wrong staging.

The prognostic value of the LNR for breast, gastric, and pancreatic cancers has been shown [10,25,26]. The association between the LNR and the course of colorectal cancers is currently being investigated, as it has not been systematically investigated so far [31,32].

In the current retrospective study, the mean duration of OS was 109.2±6.3 months (95% CI, 96.9-121.5) and the 5-year OS rate 70.3%.

The mean duration of OS in patients with a metastatic LNR <0.2 was 120.5±7.3 months (95% CI, 106.1-134.9) and the 5-year OS 75.3%.

The mean duration of OS in patients with a LNR ≥0.2 was 92.8±9.0 months (95% CI, 75.2-110.3) and the 5-year OS 64.0%. Although there was an important

clinical significance between the groups with a LNR <0.2 and ≥0.2 regarding OS, the difference did not reach statistical significance (p=0.074).

The mean duration of DFS was 87.7±6.3 months (95% CI, 75.4-100.0) and the 5-year DFS 53.1%.

The median LNR was calculated at 0.2 in the current study, and this value was considered as cut-off value.

According to the metastatic LNR, the mean duration of DFS in patients with a LNR <0.2 was 100.6±8.6 months (95% CI, 83.7-117.5). The 5-year DFS rate in patients with a LNR <0.2 was 64.1%.

The mean duration of DFS in patients with a LNR ≥0.2 was 71.7±8.3 months (95% CI, 55.4-88.0) and the 5-year DFS 44.3%. The difference between the groups with a LNR <0.2 and ≥0.2 was statistically significant (p=0.017). Thus, the LNR was shown to be a significant prognostic factor for DFS.

The number of lymph nodes evaluated, the number of positive lymph nodes, and the metastatic LNR have been investigated in studies with large sample sizes [3,7-9,23-25] showing that the LNR is an important prognostic factor in colon cancer.

The determination of the optimal cut-off value for the LNR in future prospective studies will lead to most accurate staging, as well as to more precise determination of prognosis in patients with colon cancer.

References

1. Jemal A, Tiwari RC, Murray T et al. Cancer Statistics, 2004. CA Cancer J Clin 2004; 54: 8-29.
2. Steinberg SM, Barkin JS, Kaplan RS, Stablein DM. Prognostic indicators of colon tumors: Gastrointestinal Tumor Study Group experience. Cancer 1986; 57: 1866-1870.
3. Griffin MR, Bergstralh EJ, Coffey RJ et al. Predictors of survival after curative resection of carcinoma of the colon and rectum. Cancer 1987; 60: 2318-2324.
4. Hermanek P, Wiebelt H, Riedl S et al. Long-time results of surgical therapy for colorectal cancer: results of the German Study Group for Colorectal Cancer (SGCRC). Chirurg 1994; 65: 287-297.
5. Newland RC, Chapuis PH, Pheils MT, McPherson JG. The relationship of survival to staging and grading of colorectal carcinoma: a prospective study of 503 cases. Cancer 1981; 47: 1424-1429.
6. Sigurdson ER. Lymph node dissection: is it diagnostic or therapeutic? J Clin Oncol 2003; 21: 965-967.
7. Joseph NE, Sigurdson ER, Hanlon AL et al. Accuracy of determining nodal negativity in colorectal cancer on the basis of the number of nodes retrieved on resection. Ann Surg Oncol 2003; 10: 213-218.
8. Le Voyer TE, Sigurdson ER, Hanlon 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.
9. Berger AC, Sigurdson ER, Le Voyer TE et al. Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. J Clin Oncol 2005; 23: 8706-8712.
10. Bando E, Yonemura Y, Taniguchi K et al. Outcome of ratio of lymph node metastasis in gastric carcinoma. Ann Surg Oncol 2002; 9: 775-784.
11. Lim W, Olschwang S, Keller JJ et al. Relative frequency and morphology of cancers in STK11 mutation carriers. Gastroenterology 2004; 126: 1788-1794.
12. Mandel JS, Church TR, Ederer F et al. Colorectal cancer mortality: Effectiveness of biennial screening for fecal occult blood. J Nat Cancer Inst 1999; 91: 434-437.
13. Lieberman DA, Weis DG, Bond JH et al. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. N Engl J Med 2000; 343: 162-168.
14. Turini ME, Dubois RN. Primary prevention: Phytoprevention and chemoprevention of colorectal cancer. Hematol Oncol Clin North Am 2002; 16: 811-840.
15. Steinbach G, Lynch PM, Philips RK et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med 2004; 351: 1946-1952.
16. Topol EJ. Failing the public health – Rofecoxib, Merck, and the FDA. N Engl J Med 2004; 351: 1707-1709.
17. Solomon SD, McMurray JJ, Pfeffer MA et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005; 352: 1071-1080.
18. Moertel CG, Fleming TR, Macdonald JS et al. Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report. Ann Intern Med 1995; 122: 321-326.
19. Porschen R, Bermann A, Löffler T et al. Fluorouracil plus leucovorin as effective adjuvant chemotherapy in curatively resected stage III colon cancer: results of the trial adjCCA-01. J Clin Oncol 2001; 19: 1787-1794.
20. Saltz LB, Meropol NJ, Loehrer PJ Sr et al. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. J Clin Oncol 2004; 22: 1201-1208.
21. Cunningham D, Humblet Y, Siena S et al. Cetuximab monotherapy and cetuximab plus irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004; 51: 337-345.
22. Engstrom PF, Benson AB 3rd, Chen YJ et al. Colon cancer clinical practice guidelines in oncology. J Natl Compr Canc Netw 2005; 3: 468-491.
23. Swanson RS, Compton CC, Stewart AK, Bland KI. The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. Ann Surg Oncol 2003; 10: 65-71.
24. Bui L, Rempel E, Reeson D, Simunovic M. Lymph node counts, rates of positive lymph nodes, and patient survival for colon cancer surgery in Ontario, Canada: a population-based study. J Surg Oncol 2006; 93: 439-445.
25. Berger AC, Watson JC, Ross EA, Hoffman LE. The metastatic/examined lymph node ratio is an important prognostic factor after pancreaticoduodenectomy for pancreatic adenocarcinoma. Am Surg 2004; 70: 235-240.
26. Van der Wal BC, Butzelaar RM, van der Meij S, Boermeester MA, Axillary lymph node ratio and total number of removed lymph nodes: predictors of survival in stage I and II breast cancer. Eur J Surg Oncol 2002; 9: 775-784.
27. Johnson MP, Porter AG, Ricciardi R, Baxter NN. Increasing negative lymph node count is independently associated with improved long-term survival in stage IIIB and IIIC colon can-

cer. J Clin Oncol 2006; 24: 3570-3575.
28. Kobayashi H, Ueno H, Hashiguchi Y, Mochizuki H. Distribution of lymph node metastasis is a prognostic index in patients with stage III colon cancer. Surgery 2006; 139: 516-22.
29. Schumacher P, Dineen S, Barnett JC, Fleming J, Anthony T. The metastatic lymph node ratio predicts survival in colon cancer. Am J Surg 2007; 194: 827-832.
30. 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.
31. Ogata Y, Torigoe S, Matano K et al. Prognostic factors after potentially curative resection in stage II or III colon cancer. Kurume Med J 2005; 52: 67-71.
32. Burton S, Norman AR, Brown G et al. Predictive poor prognostic factors in colonic carcinoma. Surg Oncol 2006; 15: 71-78.