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Original Article

The recurrence with isolated intra-abdominal lymph node in patients with colorectal cancer: A study of the Turkish Descriptive Oncological Researches Group (intra-abdominal lymph node and colon cancer)

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ABSTRACT

Background: This study aimed to identify the risk factors related in recurrence with isolated intra-abdominal lymph node metastasis in patients with colorectal cancer.
Methods: This is a retrospective, cross-sectional study of 21 colorectal cancer patients with isolated intra-abdominal lymph node metastases. Preoperative demographic and laboratory/postoperative histological features of these patients were been analyzed.
Results: Lymphovascular and perineural invasion and mutant-type K-ras status were more common in the study patients. In addition, a significant correlation was been detected between lymphovascular and perineural invasion, preoperative serum CEA level, preoperative thrombocyte count, mutant-type K-ras status, and pathological N3 disease. Mutant-type K-ras status and the presence of lymphovascular invasion were independent prognostic risk factors for isolated intra-abdominal lymph node metastasis.
Conclusions: The presence of lymphovascular invasion and mutant-type K-ras status may be poor prognostic risk factors for isolated intra-abdominal lymph node metastasis in patients with colorectal cancer. However, studies involving larger patient series, molecular indicators, and cohorts with metastasis in other areas are been needed to verify this study.

1. Introduction

Intra-abdominal lymph nodes are been usually dissected during curative surgery of primary colorectal cancer. It was been reported that para-aortic lymph node metastasis synchronous with primary tumor was present in 2.1% of patients with sigmoid colon cancer and in 1.9% of patients with rectal cancer.[1–3] Metachronous metastases of intra-abdominal lymph nodes, including para-aortic nodes, are been usually seen in colorectal cancer patients with widespread metastasis, together with the involvement of lungs, liver, and peritoneum.[2] However, recurrence with isolated intra-abdominal lymph node is rather rare, and the therapeutic approach to these patients is still unclear.[4] Min et al[3] reported that only 1.3% of 2916 candidates for curative surgery in colorectal cancer had isolated para-aortic lymph node metastasis. The prognosis of patients with colorectal cancer in whom recurrence occurs with isolated para-aortic lymph node metastasis is very

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poor.[2,3] In these patients, 1-year survival without any treatment is 31%, whereas 2- and 4-year survival rates are 7.9% and 0.9% respectively.[3] Although previous studies have focused on surgical treatment features of these patients, current prognostic risk factors for recurrence with isolated intra-abdominal lymph node metastasis is not clear.

In this study, we aimed to identify possible risk factors related in recurrence with isolated intra-abdominal lymph node metastasis in patients with colorectal cancer.

2. Patients and methods

2.1. Study design

This was a cross-sectional study involving 704 patients with histologically proven colorectal cancer between 2007 and 2014. Data in the files of these patients were been analyzed retrospectively. Among the patients, those with positron-emission-tomography-computed-tomography-proven (PET-CT-proven) isolated intra-abdominal lymph node metastasis were been selected as the study population. However, any a SUVmax value was not determined in the decision due to lack of accepted any knowledge on SUVmax in recurrence with isolated intraabdominal lymph node metastasis in the English literature. Additionally, histopathological confirmation for enlarged intraabdominal lymph node did not do because of surgical or interventional problems. Consequently, only 21 patients with isolated intra-abdominal lymph node recurrence were included in the study for statistical analysis.

2.2. Study variables

Baseline demographic features (age, gender); laboratory values (hemoglobin level, hematocrit value, leukocyte, neutrophils, and thrombocyte counts, and serum carcinoembryonic antigen and carbohydrate antigen 19.9 levels); postoperative histopathological characteristics (tumor grade, lymphovascular invasion, pT stage, tumor size, nodal status, perineural invasion, stage, K-ras status, and options for adjuvant treatment) of patients were recorded.

Exclusion criteria were as follows: metastasis other than intra-abdominal lymph node recurrence, receipt of neo-adjuvant treatment options (chemotherapy, radiotherapy, or chemo-radiotherapy), history of hematological malignancy, presence of a second primary solid organ malignancy, or missing file data.

Laboratory variables were as follows: hemoglobin (Hb g/dL), hematocrit (HCT %), leukocyte count (10^3/), neutrophils count (K/mL), thrombocyte count (10^3), carcinoembryonic antigen (CEA ng/mL), and carbohydrate antigen 19.9 (CA 19.9 U/mL). The Abbott Aeroset® system and ABX Pentra 120 DX® Hematology Analyzer (ABX Diagnostics, France) were been used for the measurements.

2.3. Ethics

The study protocol was been confirmed by the local ethical guidelines; the study commenced following approval of the Administrative Committee.

2.4. Statistical analysis

The data are been expressed as mean ± standard deviation or median and interquartile range (25–75%). The distribution of variables was been analyzed with the Kolmogorov–Smirnov test. Quantitative variables with normal distribution were been analyzed with a two-tailed, independent Student's t-test. Nonparametric variables were been analyzed with the Mann–Whitney U test, and the qualitative parameters were analyzed with the Chi-square and Fisher's tests. A receiver operating characteristic (ROC) curve was been performed to estimate the optimal cut-off values of preoperative CEA and CA 19.9 levels and the SUVmax level of intra-abdominal lymph node metastases measured by PET/CT. Progression-free and overall survival rates were estimated by the Kaplan–Meier method. The variables with $P < 0.05$ by univariate analysis were subjected to multivariate logistic regression analysis. In additionally, Cox's proportional hazards models analyzed multivariate analysis of patient time to death. A two-tailed result considered statistically significant $P < 0.05$.

3. Results

Recurrence with isolated intra-abdominal lymph node metastasis was diagnosed in 2.98% (n = 21) of 704 patients with colorectal cancer. The baseline demographic, clinical, and histopathological features of all patients are been presented in Table 1 and correlation analysis is been shown in Table 2.

The majority of patients (n = 17, 81%) had grade-2 tumor (n = 9, 43%), adenocarcinoma histology (n = 19, 91%), lymphovascular invasion (n = 16, 76%), perineural invasion (n = 17, 82%), pT3 (n = 11, 53%), mutant-type K-ras (n = 13, 62%), and pN3 disease (n = 7, 33%).

During the analysis, 74% (n = 16) of patients died. The mean disease-free survival time (time to isolated lymph node metastasis) was 29 ± 14 months (range 13–54), progression-free survival was 11 ± 3 months (range 8–17), and overall survival time was 32 ± 16 months (range 14–57).

For the cut-off preoperative serum CEA level of 24 ng/mL, positive predictive value was 82% and negative predictive value was 86%. In addition, the sensitivity, accuracy, and specificity of the cut-off levels were 86%, 91%, and 84%, respectively.

The mean SUVmax value of the PET/CT-proven metastatic lymph nodes was 6.9 (range 4.2–11.2). There was a significant correlation between the SUVmax values of metastatic lymph nodes and preoperative CEA levels ($r = 0.415$, $P = 0.034$), lymphovascular invasion ($r = 0.528$, $P = 0.041$), perineural invasion ($r = 0.503$, $P = 0.039$), mutant K-ras status ($r = 0.458$, $P = 0.045$), and pathological N3 disease ($r = 0.615$, $P = 0.038$). Similarly, for the SUVmax cut-off value of 6.9, overall survival times of patients with SUVmax values >6.9 were significantly shorter when compared to patients with values <6.9 (19 ± 11 and 31 ± 18 months respectively; $P = 0.032$). In addition, survival times without progression were significantly shorter in patients with SUVmax values above compared to patients with those below the cut-off (17 ± 9 and 29 ± 14 months respectively; $P = 0.043$). The most common sites for new progression in patients with SUVmax values >6.9 were the peritoneum (n = 11, 52%) and extra-abdominal distant lymph nodes (n = 9, 43%).

The independent prognostic risk factors for isolated intra-abdominal lymph node metastasis identified in the univariate analysis were the nodal status, pathological T4, presence of lymphovascular and perineural invasion, preoperative CEA, CA 19.9 levels, K-ras status, and preoperative thrombocyte count were (Table 3). The multivariate analysis showed that mutant-type K-ras status and presence of lymphovascular invasion were independent risk factors for isolated intra-abdominal lymph node metastasis (Table 3).

4. Discussion

Although the treatment of colorectal cancer patients with isolated intra-abdominal lymph node metastasis is controversial, some current studies suggest that the main treatment should be surgical excision in cases where the metastatic para-aortic lymph

Table 1
The demographical, histological, clinical, and laboratories characteristics of all patients in this study

Characteristics	n (%) or mean ± SD
n	21
Age (year)	59 ± 14
Gender	
Male	12 (57)
Female	9 (43)
Follow-up duration (month)	36 (range:14–57)
Primary tumor localization	
Ascending colon	4 (19)
Transverse colon	6 (29)
Descending colon	7 (33)
Rectosigmoid and rectum	4 (19)
Histological type	
Adenocarcinoma	19 (91)
Mucinous adenocarcinoma	2 (9)
pT	
T2	2 (9)
T3	11 (53)
T4	8 (38)
pN	
N0	3 (14)
N1	5 (24)
N2	6 (29)
N3	7 (33)
Stage	
Stage IIB	3 (14)
Stage IIIA	9 (43)
Stage IIIB	9 (43)
Tumor grade	
1	4 (19)
2	9 (43)
3	8 (38)
Lymphovascular invasion	
Absence	5 (24)
Presence	16 (76)
Perineural invasion	
Absence	4 (18)
Presence	17 (82)
Pre-operative serum CEA level	56 ± 24
Pre-operative serum CA 19.9 level	68 ± 32
Pre-operative hemoglobin level	10 ± 4
Pre-operative leukocyte count	8.1 ± 2.4
Pre-operative neutrophil count	2.7 ± 1.4
Pre-operative platelet count	498 ± 110
Adjuvant chemotherapy regimen	
FUFA (DG)	2 (10)
FUFA (MAYO)	1 (4)
FOLFOX4	8 (38)
mFOLFOX6	10 (48)
Adjuvant radiotherapy	
Radiotherapy	2 (10)
Chemo-radiotherapy	1 (5)
K-ras status	
Wild	3 (14)
Mutant	13 (62)
Unknown	5 (24)
First-line chemotherapy in metastatic setting[a]	
FOLFIRI	3
FOLFOX4	2
mFOLFOX6	1
FOLFIRI-C	3
FOLFOX4-C	2
FOLFIRI-B	5
XELOX	3
XELOX-B	2

Abbreviations: CEA, carcinoembrionic antigen; CA-19.9, carbohydrate antigen; FUFA (DG), a regimen include fluorouracil and folinic acid; FUFA (MAYO), a regimen include fluorouracil and folinic acid; FOLFOX4, a regimen include oxaliplatin, fluorouracil and folinic acid; mFOLFOX6, modified regimen include oxaliplatin, fluorouracil and folinic acid, FOLFIRI, a regimen include fluorouracil, folinic acid and irinotecan; FOLFIRI- Cetuximab, a regimen include FOLFIRI plus Cetuximab, FOLFOX4- C, a regimen include FOLFOX4 plus Cetuximab; FOLFIRI-B, a regimen include FOLFIRI plus Bevacizumab; XELOX, a regimen include Oxaliplatin and Capecitabine; XELOX-B, a regimen include XELOX plus Bevacizumab.

[a] First-line chemotherapy in metastatic setting is not include survival analyses due to heterogeneity.

Table 2
Correlation analysis of the demographic, histopathological, and clinical characteristics of patients with isolated intra-abdominal lymph node metastasis

Variables	r	P*
Age	0.211	0.223
Gender	0.204	0.247
Anatomic location of primary tumor	0.371	0.387
pT	0.325	0.278
Nodal status	0.587	0.029*
Stage	0.415	0.127
Tumor grade	0.318	0.232
Presence of lymphovascular invasion	0.511	0.036*
Presence of perineural invasion	0.456	0.046*
Pre-operative serum CEA level	0.615	0.031*
Pre-operative serum CA-19.9 level	0.274	0.215
Pre-operative hemoglobin level	0.248	0.209
Pre-operative hematocrit level	0.302	0.269
Pre-operative leukocyte count	0.245	0.238
Pre-operative neutrophils count	0.346	0.217
Pre-operative thrombocyte count	0.594	0.032*
Adjuvant chemotherapy regimen	0.295	0.364
K-ras status	0.568	0.034*

Abbreviations: CEA, carcinoembrionic antigen; CA-19.9, carbohydrate antigen-19.9.

*A two tailed P value of <0.05 was considered statistically significant.

node is localized and resectable (as in isolated liver and lung metastasis).[2–4] Considering 5-year survival rates of 30–40% after resection of liver metastasis and 48% after lung metastasis (although it is rare), second-look surgery may be preferred for selected cases with isolated intra-abdominal lymph node metastasis.[5,6] A study by Min et al[3] reported a median survival time of 34 months in colorectal cancer patients with isolated para-aortic lymph node metastasis who underwent resection after recurrence; whereas survival time was 13 months for patients who had concurrent or sequential chemotherapy together with 32.4–50.4 Gy radiation therapy or only systemic chemotherapy ($P = 0.034$). Similarly, a study by Choi et al[7] reported that median survival after lymph node dissection was 64 months (range 17–111) in colorectal cancer patients recurred with isolated para-aortic lymph node metastasis; whereas it was 33 months (range 24–42) in patients with no lymphadenectomy. Another study showed a 5-year survival rate of 53.4% for 24 patients who underwent para-aortic lymph node dissection and 12.0% for 53 patients without resection.[3–7]

However, since it is known that these patients have serious morbidity and mortality risks due to aggressive disease, bad prognosis, and involvement near the aorta, surgery may not be considered a standard treatment modality.[4,8] For this reason, the identification, complete evaluation, and individual planning of suitable treatment modalities are important.

Data in the literature shows that apart from resection surgery, stereotactic radiotherapy for selected cases may be another treatment choice.[2,7] Kim et al[2] analyzed 1- and 3-year survival rates of three fractions of 36–51 Gy stereotactic radiation therapy in rectal cancer patients who recurred with isolated para-aortic lymph node metastasis and found 100% and 71.4% survival rates respectively. Kim et al[2] calculated the mean survival time of these patients at 37 months. It was been even declared that salvage lymphadenectomy following neo-adjuvant chemotherapy might be a new therapeutic option.

In all of our patients recurred with isolated intra-abdominal lymph node metastasis, systemic therapy was the preferred treatment. The reasons for this were unsuitability of most of the patients for surgical resection due to number of metastatic lymph nodes, proximity to aorta, age, presence of co-morbidities, and insufficiency of second-look surgery as a standard treatment modality. However, when we compared the survival times of our patients

Table 3
Univariate and multivariate analyses of the factors for risk of isolated intra-abdominal lymph node metastasis in patients with colorectal cancer

	Hazard ratios (95% CI)	P value
Univariate factors		
Age (>65 vs. >65)	1.38 (0.38–3.11)	0.217
Gender (male vs. female)	1.49 (0.47–2.78)	0.231
Anatomic location of primary tumor (colon vs. rectum)	1.73 (0.93–3.08)	0.327
pT (pT2 and pT3 vs. pT4)	2.01 (1.37–5.11)	0.044*
Nodal status (N0 vs. N1 and N2 vs. N3)	1.64 (1.29–4.75)	0.038*
Stage (stage IIB and stage IIIA vs. stage IIIB)	2.14 (0.47–3.41)	0.243
Tumor grade (grade I and II vs. III)	1.98 (0.71–2.37)	0.215
Presence of lymphovascular invasion (absence vs. presence)	2.33 (1.59–6.98)	0.017*
Presence of perineural invasion (absence vs. presence)	2.27 (1.94–7.12)	0.029*
Pre-operative serum CEA level (<24 ng/mL vs. >24 ng/mL)[a]	1.66 (1.23–5.27)	0.034*
Pre-operative serum CA-19.9 level (<54 U/mL vs. >54 U/mL)[a]	1.48 (1.23–4.18)	0.041*
Pre-operative hemoglobin level (decreased vs. normal)	1.97 (1.47–3.28)	0.272
Pre-operative hematocrit level (decreased vs. normal)	1.44 (1.33–2.49)	0.214
Pre-operative leukocyte count (increased vs. normal)	1.99 (1.61–3.16)	0.364
Pre-operative neutrophils count (increased vs. normal)	1.42 (1.17–3.16)	0.287
Pre-operative thrombocyte count (increased vs. normal)	2.37 (1.49–45.29)	0.037*
K-ras status (mutant vs. wild)	2.68 (1.67–11.48)	0.014*
Multivariate factors		
Presence of lymphovascular invasion	1.98 (1.67–6.08)	0.027*
Mutant-type K-ras status	3.47 (1.61–11.25)	0.021*

Abbreviations: CI, Confidence intervals; CEA, carcinoembrionic antigen; CA-19.9, carbohydrate antigen.
*A two tailed P value of <0.05 was considered statistically significant.
[a] Cut-off values.

with the literature cases who had undergone surgical resection, we found that the mean survival times of our cases were been shorter compared to the patients who underwent surgery.[3–8] We believe our survival times are similar to that of colorectal cancer patients presented in the literature, who recurred with isolated lymph node metastasis and were been treated with systemic chemotherapy and targeting molecular agents. The response rates and prognostic features of these patients were been not considered, as our study aimed to identify risk factors. It is unclear which treatment regimen should be used for cases recurred with isolated intra-abdominal lymph node metastasis.[9,10] However, we suggest that, as a general principle, treatment regimen can been planned according to age, co-morbidities, performance, and K-ras status of the patient. Fuji et al[9] also presented an older patient with rectum cancer in whom complete response was been achieved with oral tegafur/uracil treatment. Tsuchiya et al[10] reported a similar case of a 66-year old colon cancer patient, declaring that complete response was been achieved with uracil/tegafur plus leucovorin treatment.

It was been also shown some risk factors on poor prognosis including stage, nodal metastasis, lymphovascular invasion, perineural invasion, and histological type. In addition, preoperative CEA level was closely related to distant metastasis.[11–13]

Nodal status is been accepted as one of the most important prognostic features, and a relationship between lymphovascular invasion and nodal stage was shown.[11] Unlike local lymph node metastasis, the mechanism of distant lymph node metastasis and factors affecting it are unclear.[11,12] Our study showed that lymphovascular invasion was an important independent risk factor for recurrence with isolated intra-abdominal lymph node metastasis. However, the effect of nodal status on these patients at the time of diagnosis could not be determined in the multivariate analysis.

The K-ras gene mutation is been detected in about 30% of patients with colorectal cancer. Some authors suggest the mutation in colorectal cancer is been related to multiple liver and lung metastasis and shows bad prognostic features.[13–18] However, the relationship between K-ras status of primary tumor and stage at the time of diagnosis is unclear.[16,17] In our study, we detected K-ras mutation in 62% of 21 colorectal cancer patients who recurred with isolated intra-abdominal lymph node metastasis. We revealed that mutant-type K-ras status is an important risk factor for recurrence with isolated intra-abdominal lymph node metastasis. Since this study was retrospective, it included some patients with unknown K-ras status, and N-ras status was been not examined; therefore, this result is hypothetical.

The most important limitations of our study were relatively low number of patients, undetermined effects on prognosis, unknown K-ras status of some patients, and absence of predictive biomarkers.

In this retrospective cross-sectional study, 21 colorectal cancer patients with isolated intra-abdominal lymph node metastasis were been evaluated for clinical and histopathological characteristics. In the analysis, mutant-type K-ras status and presence of lymphovascular invasion were been identified as risk factors for isolated intra-abdominal lymph node metastasis. However, these results should been clarified by larger studies that include sufficient numbers of patients.

Conflicts of interest

The author reports no conflicts of interest.

References

1. Biasco G, Derenzini E, Grazi G, et al. Treatment of hepatic metastases from colorectal cancer: Many doubts, some certainties. *Cancer Treat Rev*. 2006;32:214–218.
2. Kim MS, Cho CK, Yang KM, et al. Stereotactic body radiotherapy for isolated paraaortic lymph node recurrence from colorectal cancer. *World J Gastroenterol*. 2009;15:6091–6095.
3. Min BS, Kim NK, Sohn SK, et al. Isolated paraaortic lymph-node recurrence after the curative resection of colorectal carcinoma. *J Surg Oncol*. 2008;97:136–140.
4. Nishimura G, Funaki H, Michiwa Y, et al. A case of a combined aortectomy with dissection of recurrent paraaortic lymph nodes of sigmoid colon cancer (in Japanese with English abstract). *Jpn J Cancer Chemother*. 2000;27:2001–2004.
5. Galandruk S, Wieand HS, Maertel CG, et al. Patterns of recurrence after curative resection of carcinoma of the colon and rectum. *Surg Gynecol Obstet*. 1992;174:27–32.
6. Sugarbaker PH. Second-look surgery for colorectal cancer: Revised selection factors and new treatment options for greater success. *Int J Surg Oncol*. 2011:8. http://dx.doi.org/10.1155/2011/915078. ID 915078.
7. Choi PW, Kim HC, Kim AY, et al. Extensive lymphadenectomy in colorectal cancer with isolated para-aortic lymph node metastasis below the level of renal vessels. *J Surg Oncol*. 2010;101:66–71.

8. Hashimato M, Komatsu H, Naruse Y, et al. Resection of paraaortic lymph node metastasis of colon cancer with graft replacement. *Hepato-Gastroenterol*. 2003;50:709–710.
9. Fujii S, Ota M, Ichikawa Y, et al. Paraaortic lymph node metastasis showed CR to UFT/LV therapy in elderly rectal cancer. *Hepato-Gastroenterol*. 2010;57:472–476.
10. Tsuchiya N, Yamagishi S, Ishibe A, et al. A case of para-aortic lymph node metastasis from colon cancer with complete response to uracil/tegafur plus leucovorin therapy. Gan to kagaku ryoho. *Cancer Chemother*. 2014;41:261–263.
11. Schneider NI, Langner C. Prognostic stratification of colorectal cancer patients: Current perspectives. *Cancer Manag Res*. 2014;6:291–300.
12. Fujii T, Tabe Y, Yajima R, et al. Process of distant lymph node metastasis in colorectal carcinoma: Implication of extracapsular invasion of lymph node metastasis. *BMC Cancer*. 2011;11:216. http://dx.doi.org/10.1186/1471-2407/11/216.
13. Nielsen HJ, Christensen IJ, Brunner N. A novel prognostic index in colorectal cancer defined by serum carcinoembryonic antigen and plasma tissue inhibitor of metalloproteinases-1. *Scand J Gastroenterol*. 2010;45:200–207.
14. Arrington AK, Heinrich EL, Lee W, et al. Prognostic and predictive roles of KRAS mutation in colorectal cancer. *Int J Mol Sci*. 2012;13:12153–12168.
15. Cejas P, Lopez-Gomez M, Aguayo C, et al. KRAS mutations in primary colorectal cancer tumors and related metastases: A potential role in prediction of lung metastasis. *PLoS One*. 2009;4:e8199.
16. Andreyev HJ, Norman AR, Cunningham D, et al. Kirsten ras mutation in patients with colorectal cancer: The "RASCAL Ilé study. *Br J Cancer*. 2001;85:692–696.
17. Santini D, Loupakis F, Vincenzi B, et al. High concordance of KRAS status between primary colorectal tumors and related metastatic sites: Implications for clinical practice. *Oncol*. 2008;13:1270–1275.
18. Nash GM, Gimbel M, Shia J, et al. KRAS mutation correlates with accelerated metastatic progression in patients with colorectal liver metastases. *Ann Surg Oncol*. 2010;17:572–578.