

Modern Chemotherapy Mitigates Adverse Prognostic Effect of Regional Nodal Metastases in Stage IV Colorectal Cancer

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Abstract

Background In colorectal cancer, the involvement of regional lymph nodes with metastasis is an established prognostic factor. The impact of the number of positive nodes on patient outcome with stage IV disease is not well defined.

Methods A retrospective review was performed of 1,421 patients at two tertiary referral centers with stage IV colorectal cancer who underwent primary tumor resection. Associations between regional nodes, lymph node ratio (LNR), and overall survival (OS) from date of diagnosis were analyzed.

Results The number of positive regional nodes and LNR correlated with multiple sites of metastases ($p < 0.001$). Survival was significantly associated with the number of positive nodes and LNR, with a median OS of 43 months with negative nodes, compared to 20 months with ≥ 7 positive nodes ($p < 0.001$). The number of regional nodal metastases correlated with OS among 400 patients undergoing resection of liver metastases ($p = 0.005$) but lost prognostic significance in the subset of 223 patients who underwent hepatectomy with perioperative oxaliplatin- or irinotecan-based chemotherapy ($p = 0.48$).

Conclusions In stage IV colorectal cancer, an increasing number of positive regional nodes and LNR correlate with multiple sites of metastases and poorer survival. The number of metastatic regional lymph nodes loses prognostic significance with modern chemotherapy in patients undergoing resection of liver metastases.

Keywords Lymph nodes · Metastases · Colorectal cancer

Introduction

In patients with non-metastatic colorectal cancer, the most important prognostic factor is lymph node involvement, and

adjuvant chemotherapy is recommended for stage III disease. In addition to the number of positive regional nodes, the number of lymph nodes harvested and pathologically examined determines prognosis in localized disease. In stage IV colorectal cancer, the prognostic effect of regional nodal metastases and the ratio of metastatic to examined lymph nodes, the lymph node ratio (LNR), is unclear. Two studies on nomograms for estimating survival after resection of colorectal liver metastases demonstrated an adverse effect of positive regional lymph nodes on patient survival.^{1,2} However, neither study specifically examined patients treated with modern oxaliplatin- or irinotecan-based chemotherapy. These cytotoxic regimens, in combination with biologic agents, have improved response rates and doubled median survival in stage IV colorectal cancer.³ In patients undergoing resection of liver metastases, modern chemotherapy has abrogated the impact of traditional prognostic factors, such as size and number of metastases.^{4,5} This study aimed to determine the significance of the number of regional nodal metastases and LNR in patients with stage IV colorectal cancer, particularly among

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those undergoing potentially curative resection of hepatic metastases.

Methods

Following approval by the respective Institutional Review Boards, medical records were retrospectively reviewed of patients with stage IV colorectal cancer evaluated at the Mayo Clinic during the period 1991 to 2008 ($n=743$) and Fox Chase Cancer Center during the period 2000 to 2011 ($n=678$). All patients underwent resection of their primary tumors with curative intent or for palliation of symptoms. Exclusion criteria included two concurrent primary malignancies, histology other than adenocarcinoma, and appendiceal carcinoma. Synchronous disease was defined as distant metastases identified within 6 months of primary colorectal cancer diagnosis.⁶ The extent of metastatic disease was based upon operative and radiology reports. Initial sites of metastases at the time of stage IV diagnosis, but not subsequent sites, were recorded.

Pathologic staging was classified according to the seventh edition of the American Joint Committee on Cancer (AJCC) staging system. Stage IV nodal metastases were defined as retroperitoneal, hepatic pedicle, thoracic, or other lymph nodes (i.e., supraclavicular, inguinal) remote from the regional nodal basin of the primary tumor diagnosed by radiographic imaging or surgical exploration. For statistical analysis, LNR was categorized into four separate quartiles: <0.05 , $0.05-0.19$, $0.2-0.39$, and $0.4-1$. Patients were considered to have received “modern” chemotherapy if they were treated with oxaliplatin- or irinotecan-based chemotherapy within 3 months of stage IV diagnosis. For the purposes of this study, treatment with capecitabine or hepatic arterial infusion with floxuridine was categorized as “non-modern” 5-fluorouracil (5-FU)-based chemotherapy. More patients in the latter part of the study period received modern chemotherapy, compared to 5-FU. Among patients administered 5-FU, the percentage of patients treated between the years 1991 and 1999 was 28 %, compared to 53 % between 2000 and 2005 and 19 % between 2006 and 2011. Among patients administered modern chemotherapy, 13 % were treated between 1991 and 1999, 43 % between 2000 and 2005, and 44 % between 2006 and 2011. Radiofrequency ablation of liver metastases, with or without hepatectomy, was categorized as an R1 resection.

Statistical analysis was performed using SPSS software, version 12.0, SPSS Inc., Chicago, IL, USA. Survival times were calculated from date of stage IV diagnosis to date of death or last follow-up. Colorectal cancer-specific survival curves were generated according to the Kaplan-Meier method and were compared using the log-rank test. Categorical variables were compared using the chi-square test. Differences were considered statistically significant when the p value was <0.05 .

Results

Clinicopathologic characteristics of 1,421 patients who underwent resection of their primary tumors and were diagnosed with stage IV colorectal cancer are presented in Table 1. Median follow-up for all patients was 23 months (range 1–211 months). Most patients presented with synchronous stage IV disease and had primary tumors located in the colon. Modern oxaliplatin- or irinotecan-based chemotherapy was administered to 54 % of patients within 3 months of their stage IV diagnosis.

Sites of metastases are presented in Table 2. The most common sites of metastases were the liver, multiple, peritoneum, and lung. Among 400 patients with multiple sites of metastases, 329 patients (82 %) had two sites, 52 (13 %) had three sites, 16 (4 %) had four sites, 2 (0.5 %) had five sites, and 1 patient (0.3 %) had eight sites involved by metastatic disease.

Table 1 Clinicopathologic characteristics of 1,421 patients, n (%)

Characteristic	Value
Median age, years (range)	62 (18–94)
Male gender	776 (55)
Year of stage IV diagnosis	
1991–1999	408 (29)
2000–2005	564 (40)
2006–2011	449 (31)
Primary tumor location	
Colon	1,154 (81)
Rectum	267 (19)
Stage IV presentation	
Synchronous	1,140 (80)
Metachronous	281 (20)
No. of sites of metastases, median (range)	1 (1–8)
Serum CEA at stage IV diagnosis, median (range, ng/ml) ^a	13.9 (0.2–41,375.0)
Median number of positive regional lymph nodes (range)	3 (0–41)
Median number of harvested lymph nodes (range)	13 (0–98)
Median lymph node ratio (range)	0.25 (0.0–1.0)
AJCC 7th edition N groups	
N0	288 (20)
N1a (1 node)	206 (15)
N1b (2–3 nodes)	306 (21)
N2a (4–6 nodes)	306 (21)
N2b (≥ 7 nodes)	315 (22)
Chemotherapy within 3 months of stage IV diagnosis	939 (66)
5-Fluorouracil-based	169 (12)
Oxaliplatin- or irinotecan-based	770 (54)

CEA carcinoembryonic antigen, AJCC American Joint Committee on Cancer

^aData available in 713 patients

Table 2 Sites of metastases

	<i>n</i> = 1,421	Percent
Liver	739	52
Peritoneum	133	9
Lung	83	6
Distant lymph nodes	46	3
Ovary	10	0.7
Abdominal wall	5	0.4
Brain	2	0.1
Adrenal	2	0.1
Head of pancreas	1	0.07
Multiple	400	28

An increasing number of positive regional nodes ($p < 0.001$) and higher LNR ($p < 0.001$) correlated with the presence of multiple sites of distant metastases (Fig. 1). Among patients with negative regional nodes, 20 % had multiple sites of metastases, compared to 38 % of patients with ≥ 7 positive regional nodes.

Overall survival (OS) was significantly associated with the number of positive regional lymph nodes (Fig. 2). Similarly, median OS with LNR < 0.05 was 42 months (95 % confidence interval (CI) 37–47 months), which was significantly longer than that with a LNR of 0.4–1.0 (19 months, 95 % CI 15–22 months) ($p < 0.001$).

Metastectomy was performed in 520 patients, including resection of the liver, lung, peritoneum, ovary, and/or distant lymph nodes (Table 3). Multiple sites of metastases were resected in 28 patients. R0 resection was achieved in most patients except those undergoing peritoneal metastasectomy. Among patients undergoing resection of hepatic, pulmonary, or peritoneal metastases, median survival was significantly improved with modern chemotherapy (all $p < 0.05$). Modern

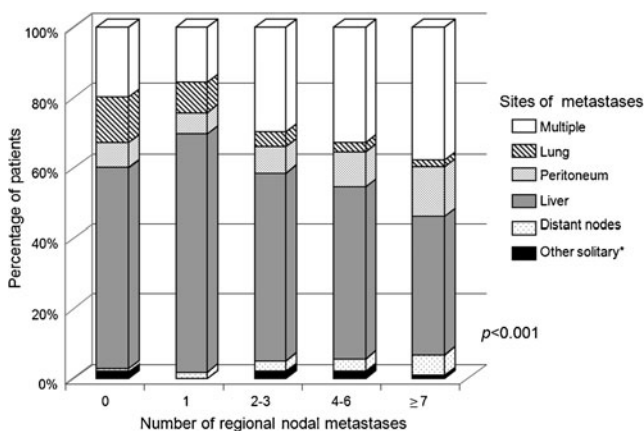


Fig. 1 Increasing number of positive regional lymph nodes correlated with the presence of multiple sites of distant metastases. The *asterisk* in the legend denotes other sites of solitary metastasis including the ovary, abdominal wall, brain, adrenal, and head of pancreas

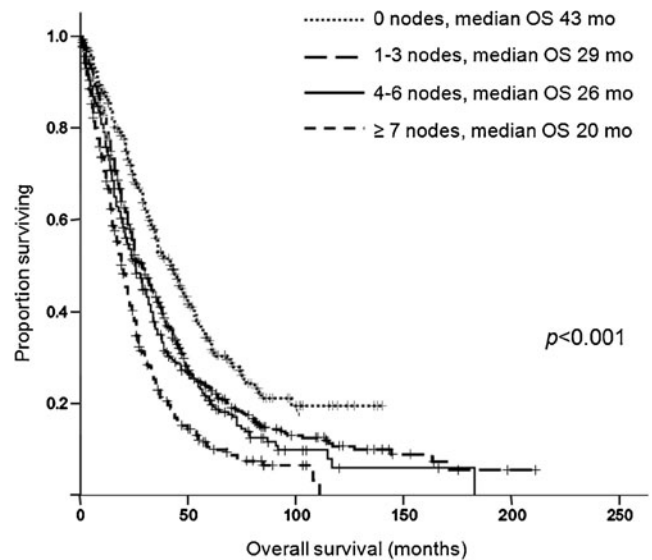


Fig. 2 Overall survival among 1,421 patients with stage IV colorectal cancer correlated with the number of positive regional lymph nodes. OS overall survival

chemotherapy was not significantly associated with improvement in survival among the small numbers of patients undergoing resection of distant nodal or ovarian metastases ($p > 0.1$)

Among 400 patients who underwent hepatectomy, median OS was 81 months (95 % CI 57–105 months) with negative regional lymph nodes, compared with 42 months (95 % CI 31–53 months) with ≥ 7 regional nodes ($p = 0.005$) (Fig. 3a). Subgroup analysis of 223 patients who underwent liver resection with perioperative modern chemotherapy showed that the median OS with negative regional nodes was 76 months (95 % CI 65–84 months), which was similar to that with ≥ 7 regional nodes (85 months, 95 % CI 22–148 months, $p = 0.48$) (Fig. 3b). Among 73 patients undergoing liver resection with perioperative 5-FU-based chemotherapy, without irinotecan or oxaliplatin, the number of regional lymph nodes remained a significant predictor of survival ($p < 0.001$).

Discussion

In localized colorectal cancer, lymph node metastasis is the most important prognostic factor and determines the need for adjuvant therapy following surgical resection. Survival decreases with not only the presence of positive nodes but also their number. In stage IV disease, the prognostic effect of the number of positive regional lymph nodes is not well established.^{1,7,8} In patients undergoing resection of colorectal liver metastases, prognostic scoring systems have identified lymph node positivity of the primary tumor as a predictor of outcome.⁷ However, the relevance of risk scoring systems has been questioned in the current era of effective systemic chemotherapy.⁹ In the present study, an increasing number

Table 3 Data on 520 patients who underwent metastasectomy, *n* (%)

Site	R status			Median OS without modern chemotherapy (95 % CI), mo	Median OS with modern chemotherapy (95 % CI), mo
	R0	R1	R2		
Liver, <i>n</i> =400	282 (71)	117 (29)	1 (0.3)	46 (38–54)	71 (55–87)
Lung, <i>n</i> =66	58 (88)	7 (11)	1 (1)	17 (13–21)	43 (0–88)
Peritoneum, <i>n</i> =40	18 (45)	19 (48)	3 (7)	18 (14–22)	36 (29–43)
Ovary, <i>n</i> =29	29 (100)	0	0	15 (6–24)	37 (20–54)
Lymph nodes, <i>n</i> =21	20 (95)	1 (5)	0	44 (0–103)	33 (30–36)

OS overall survival, *mo* months

of positive regional lymph nodes and lymph node ratio (LNR) correlated with multiple sites of distant metastases. In addition, overall survival was significantly associated with higher number of positive nodes and LNR. The number of regional nodal metastases correlated with survival among patients undergoing resection of liver metastases but lost prognostic significance in the subset patients who underwent hepatectomy with perioperative oxaliplatin- or irinotecan-based chemotherapy.

Our findings support a previous study by Cardona et al., which examined the prognostic effect of primary tumor-related factors in patients undergoing resection of colorectal liver metastases.¹⁰ On multivariate analysis, patients with lymphovascular invasion and >3 positive regional nodes had significantly lower survival than patients without lymphovascular invasion or regional nodal involvement. In the current study, among all patients who did and did not undergo resection of their metastases, a significant difference in survival was observed between patients with node-negative and N2b disease (≥ 7 positive nodes), whose median survival rates were 43 and 20 months, respectively. Smaller differences in median survival rates were seen between N1 (one to three

nodes) and N2a (four to six nodes) disease of 29 and 26 months, respectively.

The key finding of this study is that the number of regional nodal metastases correlates with survival after resection of colorectal liver metastases but loses prognostic significance among patients treated with perioperative oxaliplatin- or irinotecan-based chemotherapy. These results support other reports showing that traditional prognostic factors, such as number and size of liver metastases, are less relevant in the current era of effective cytotoxic and biologic agents.^{5,11} In a study by Blazer et al. of patients treated with oxaliplatin- or irinotecan-based chemotherapy before resection of colorectal liver metastases, the primary tumor lymph node status was not associated with patient survival.⁴ On multivariate analysis, only surgical margin status and pathologic response to preoperative chemotherapy were independent predictors of survival. Our results suggest that effective modern chemotherapy abrogates the negative prognostic effect of regional nodal metastases by potentially eradicating micrometastases, improving patient selection for surgery when administered preoperatively, and downsizing metastases to enable more patients to undergo R0 resection.

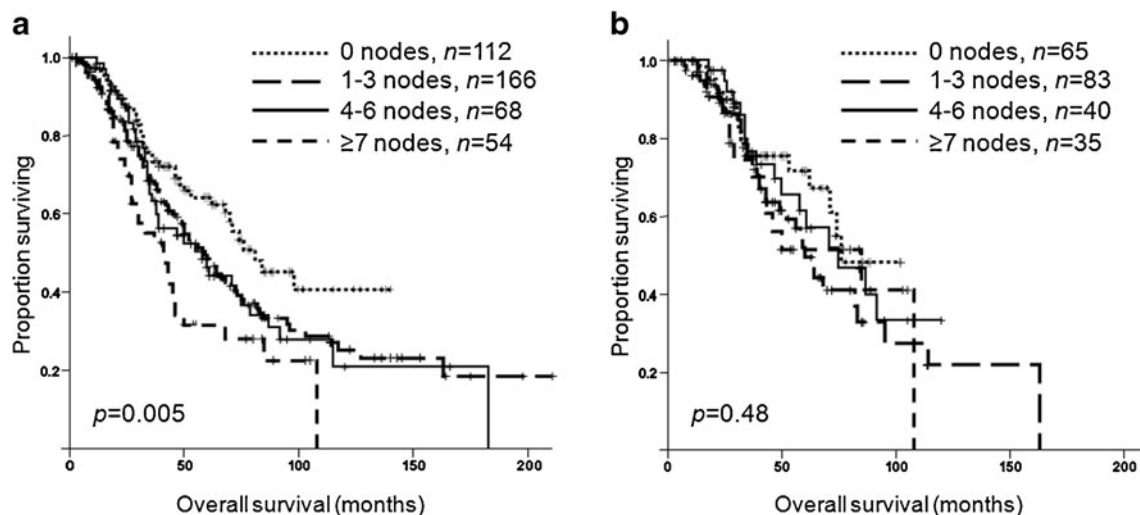


Fig. 3 Overall survival by number of positive regional lymph nodes among **a** 400 patients undergoing resection of colorectal liver metastases and **b** subset of 223 patients administered perioperative modern chemotherapy

Our data underscore the prognostic significance of not only the number of positive regional nodes but also the LNR in stage IV colorectal cancer. In non-metastatic colon cancer, staging accuracy and oncologic outcomes are improved with higher nodal retrieval and histopathologic examination.¹² The prognostic effect of positive regional nodes depends upon the number of nodes analyzed, and the LNR normalizes for the inconsistencies in lymph node retrieval and evaluation.¹³ Similar to our findings, previous studies of stage IV disease have demonstrated significant associations between LNR and survival, as well as between LNR and the presence of multiple sites of metastases.^{14,15} Collectively, these results suggest the importance of adequate lymph node harvesting and pathologic examination in metastatic colorectal cancer.

Limitations of this study include its retrospective nature and small numbers of patients undergoing resection of extrahepatic metastases. Our data demonstrate that regional nodal involvement is not associated with survival among patients undergoing resection of liver metastases with perioperative modern chemotherapy. In these patients, regional lymph nodes lost prognostic significance because of not only the effects of modern chemotherapy but also additional selection factors for hepatic resection in the modern era, including high-quality imaging, intraoperative ultrasonography, and improved surgical techniques. The number of patients is too small to form conclusions about resection of extrahepatic disease, such as pulmonary and peritoneal metastases. In addition, most patients in our study had synchronous stage IV disease, which reflects our query of institutional tumor registries for patients with stage IV colorectal cancer.

In conclusion, this study demonstrates the prognostic significance of regional nodal metastases in stage IV colorectal cancer. An increasing number of positive regional lymph nodes and LNR correlated with multiple sites of metastases and overall survival. Among patients undergoing resection of liver metastases, the number of regional nodes remained a significant prognostic factor, but in the subset of patients who underwent hepatectomy with perioperative modern chemotherapy, the number of regional nodes did not correlate with patient outcome. Thus, patients who are eligible for potentially curative liver resection should not be denied surgery because of a high number of positive regional nodes.

Conflict of Interest The authors do not have any relevant relationships to disclose.

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Discussant

Dr. J. Nicolas Vauthey (Houston, TX, USA): The authors should be congratulated for presenting another paper indicating the absence of prognostic value of the status of primary lymph

nodes in patients undergoing resection of colorectal liver metastases after receiving preoperative modern oxaliplatin- or irinotecan-based chemotherapy. This paper may explain why studies have increasingly shown limited value in this new era of preoperative chemotherapy of the scores developed in the 1990s to predict the survival of patients undergoing resection of colorectal liver metastases.

The authors of this paper have presented two very different cohorts of patients with metastatic colorectal cancer: those who did not and those who did undergo resection of their metastases. The patients who did not undergo resection are an unselected group, while the patients who did undergo resection are a doubly selected group—i.e., patients who were selected on the basis of good response to chemotherapy and who then were selected for resection on the basis of multiple factors. Therefore, it is likely that not only “modern chemotherapy” but also additional selection tools such as high-quality imaging, a longer duration of preoperative chemotherapy, and improved intraoperative ultrasonography and surgical techniques all contributed to the observed similar survivals irrespective of primary nodal status. I have two sets of questions for the authors:

1. What are the authors' current recommendation regarding perioperative adjuvant chemotherapy in patients with colorectal liver metastases? Should all patients receive preoperative chemotherapy as a selection tool prior to resection? Should some patients be considered for up-front surgery without preoperative chemotherapy?

2. Recent studies have indicated a lack of predictive value of colorectal risk scores or other prognostic models in the new era of preoperative chemotherapy for colorectal liver metastases. Considering the wide range of biologic responses often seen with preoperative chemotherapy, which prognostic tools should be used now or evaluated in the future to predict the

prognosis of patients undergoing resection of colorectal liver metastases?

Closing Discussant

Dr. Alan Thomay: We greatly appreciate Dr. Vauthey's thoughtful review of the manuscript and insightful questions. Our bias at Fox Chase Cancer Center is to administer preoperative oxaliplatin- or irinotecan-based chemotherapy to most patients with colorectal liver metastases, based on the results of the EORTC 40983 trial. We limit the amount of preoperative chemotherapy to 4–6 cycles because of potential chemotherapy-associated hepatotoxicity. We favor up-front surgery for patients with small, solitary metastases that may disappear radiographically with preoperative chemotherapy. In addition, we avoid preoperative chemotherapy in patients with residual neuropathy from prior oxaliplatin or who have a contraindication to treatment with irinotecan, particularly steatohepatitis.

Regarding prognostic tools, rather than traditional criteria such as size and number of hepatic metastases, we use radiologic and pathologic responses to preoperative chemotherapy, which are independent predictors of survival, as shown by Dr. Vauthey and colleagues at M. D. Anderson. In addition, the M. D. Anderson group has demonstrated that patients treated with adjuvant FOLFOX after resection of colorectal cancer who then develop metachronous liver metastases are more likely to harbor *KRAS* mutations in their liver metastases (Andreou A et al. *Annals of Surgery* 2012). These patients have inferior survival after hepatic resection compared to those treated with 5-FU only after primary tumor resection. Other molecular markers will likely emerge as important prognostic factors in our new era of preoperative chemotherapy.