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ADJUVANT TREATMENT OF EARLY COLON CANCER WITH MICROMETASTASES: RESULTS OF A NATIONAL SURVEY

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Abstract

Background and Objectives—Optimal adjuvant treatment for patients with stage I/II colon cancer with micrometastases (MM) is unknown. Because there is no known adjuvant treatment-related benefit, we evaluated whether MM influenced treatment decisions.

Method—Review of a national survey from members of the SSO and ASCO.

Results—Of 602 survey responses, 305 (51%) stated that MM had significant prognostic value, 250 (42%) were unsure, and 47 (7%) did not believe that MM held prognostic value. Three hundred seventy-four (63%) would offer adjuvant therapy in the setting of MM, while 222 (37%) would not. Only 15% routinely performed IHC on lymph nodes. Medical oncologists were more likely to recommend adjuvant therapy compared to surgical oncologists (68% vs. 51%, $p=0.001$).

Conclusions—MM in colon cancer apparently influenced adjuvant treatment decisions absent known prognostic benefit. Prospective trials are needed to improve the selection of patients for systemic chemotherapy in early, node-negative colon cancer.

Keywords

Colon Cancer; Lymph Node Metastases; Micrometastatic Disease; Adjuvant Chemotherapy

Introduction

Patients with no evidence of lymph node metastases by conventional hematoxylin and eosin (H&E) staining have been found to have occult metastases detected by immunohistochemistry (IHC) in 32% to 76% of patients^{1,2}. The prognostic role of micrometastatic (MM) disease in Stage II colon cancer (CC) remains controversial.

Liefers and Bosch demonstrated decreased survival in a small group of node negative (N0) patients with evidence of MM disease detected by polymerase chain reaction (PCR)^{3,4}. More recent studies including a prospective randomized trial by Fisher et al.⁵ and a meta-analysis by Iddings⁶ failed to find any significant difference in survival in patients with MM detected by IHC although there was a survival difference in MM detected by PCR.

There is considerable debate about the use of adjuvant chemotherapy in patients with Stage II CC because randomized trials⁷ have suggested improved disease-free survival in a subset of patients with clinical and molecular high risk features that are at higher risk of disease recurrence that benefit from chemotherapy. However, it is unclear whether patients with MM represent a high-risk group and whether they would benefit from adjuvant chemotherapy. We evaluated whether MM influenced clinical treatment decisions in a national survey assessing treatment preferences amongst members of the Society of Surgical Oncology (SSO) and the American Society of Clinical Oncology (ASCO).

Materials and Methods

A survey was designed by the authors of this study, which was aimed at assessing practice patterns when confronted with Stage II colon cancer with MM disease in the lymph nodes. The survey was beta-tested on experienced surgical oncologists for face validity and usability. The final version of this survey was constructed and disseminated to 4000 members of the SSO and ASCO.

The invitation to participate in the survey was distributed to the SSO and ASCO members via electronic newsletter. The survey consisted of eight eligibility questions, and ten questions in the body of the survey, in a combination of multiple choice and forced choice formats (Table 1). All questions were in a fixed order and respondents were allowed to change any answer prior to final submission. No financial award or incentive was provided. All survey responses were collected anonymously and were not tracked by origin or IP address.

The questionnaire contained a case presentation that described a patient with node negative CC with MM. All research related activities were approved by the Cedars Sinai Medical Center Institutional Review Board (IRB # 23249). A 54-year-old male was described who underwent a left hemicolectomy for colon adenocarcinoma. Pathology revealed a T2, 2cm, moderately differentiated adenocarcinoma with 14 lymph nodes negative by routine hematoxylin and eosin (H&E) staining. Further evaluation of the lymph nodes by IHC revealed evidence of MM disease. The patient was staged as T1N0i+. Questions concerning practice preference and demographic data followed.

Statistical Analysis

All data was entered into a standardized database program (Microsoft Excel®, Seattle, WA). Questionnaire responses were tabulated and analyzed by chi square analysis. A *P* value of 0.05 was considered statistically significant.

Results

Response Rate and Demographics

In total, 602 of the 4000 (15%) of questionnaires were completed. Of the respondents, 304 (50%) were medical oncologists (MO), 156 (26%) surgical oncologists (SO), 115 (19%) pathologists, and 27 (5%) from other specialties (Table 2). This represented a large geographic distribution with 87 (20%) from the Northeast, 81 (19%) from the Southeast, 82 (19%) from the Midwest, 75 (17%) from the Southwest, 17 (4%) from the Northwest, and 89 (21%) from outside the United States. Practice experience varied with 96 (16%) in practice less than 5 years, 142 (24%) for 5 to 10 years, and 364 (60%) in practice greater than 10 years. Two hundred ninety-two (49%) were community practitioners and 289 (48%) were from academic institutions (Table 2).

Effect of MM Disease on Prognosis and Therapy

Of the 602 respondents 305 (51%) reported that MM disease had prognostic value; 250 (42%) were unsure (Table 3). One hundred seventy-eight (30%) of the respondents did not think that MM should impact staging while 123 (20%) thought MM should confer a special staging category (N0-1) (Table 3). Three hundred one (50%) reported that the presence of MM disease should upstage patients from N0 to N1 (AJCC Stage III) disease. Three hundred seventy-four (62%) would offer adjuvant chemotherapy to a patient with MM who would otherwise be considered stage II. Despite this, 511 (85%) did not routinely perform IHC and only 391 (65%) felt the number of resected lymph nodes were clinically relevant (Table 3).

Comparing Groups

Significant difference in practice patterns was noted when comparing MO to SO (Table 4). More MO's than SO's felt MM disease held prognostic value 53% vs. 47% ($p=0.04$). Opinions differed on staging classification with 52% of MO's believing MM conferred N1 (Stage III) status vs. 40% of SO's ($p=0.02$). Two-thirds (68%) of MO's would offer adjuvant chemotherapy compared with 51% of SO's ($p=0.001$) in the setting of MM disease alone (N0i+) (Table 4).

Discussion

More than 150,000 cases of colorectal cancer are diagnosed annually⁸ in the United States with a relatively equal distribution between stage I and IV disease. Distinguishing between Stage II and Stage III disease has important treatment implications since the majority (~75%) of Stage II CC are cured by surgical resection alone while those with Stage III CC benefit from adjuvant chemotherapy.

Despite significant progress in the discovery of more effective adjuvant therapeutic agents recurrence rates remain at approximately 20–25% among patients with Stage II⁹ disease. Several studies have been performed in order to improve diagnostic and prognostic criteria in an effort to improve clinical decision-making regarding adjuvant therapy in Stage II CC. These include assessment of adequate lymphadenectomy¹⁰, sentinel lymph node evaluation¹¹, staining with IHC to identify MM disease and most recently molecular signatures¹².

Survival is impacted by the number of lymph nodes retrieved and this has resulted in the implementation of quality measures by the National Quality Forum^{13,14}. However, it is unclear whether the quality improvements are related to improved surgical techniques or more comprehensive pathologic evaluation¹⁵. Performance of adequate lymphadenectomy confounds some earlier data evaluating MM disease where inadequate resection was routinely performed. The challenge remains to define the high risk sub-groups amongst Stage II patients with CC that are most likely to benefit from chemotherapy.

In the MOSAIC trial¹⁶ which was pivotal in the approval of oxaliplatin chemotherapy in the adjuvant setting, high-risk was defined in a pre-determined fashion as T4 disease, tumor perforation, poorly differentiated histology, lymphovascular invasion, inadequate lymphadenectomy, or obstruction. MM was not evaluated as a potential prognostic factor in this study, particularly in the setting of adequate lymphadenectomy (12LN's).

Messerini¹⁷ performed a pathologic assessment of 395 consecutive patients undergoing curative resection with pT3N0M0 disease (staged using conventional histopathology) and greater than 15 lymph nodes retrieved. There were no significant survival differences between patients with or without MM disease at a median follow up time of 128 months. However, lack of methodological standardization when performing IHC makes it difficult to compare studies that report outcomes associated with nodal MM disease in CC¹⁸. Therefore, it is surprising that despite lack of convincing data in the literature most oncologists supported MM as a prognostic factor that should result in up staging of patients with CC.

Currently, it is standard practice to offer adjuvant chemotherapy to patients with Stage III disease¹⁹. Since the majority of respondents in our survey equated MM with a higher stage it is not surprising that most would also offer adjuvant therapy. Somewhat unexpected were the differences noted between respondents according to subspecialty - MO versus SO. As a whole, MO's were more likely to view MM as a negative prognostic factor in CC, and were more likely than SO's to upstage patients, and offer adjuvant therapies on that basis. While it is unclear why significant differences in opinion exist between MO and SO, only 15% recommended routine evaluation of lymph nodes by IHC.

Difference in opinion may be associated with philosophical differences between MO's and SO's or the over-interpretation of numerous conflicting studies. Discordance in therapy between SO and MO has also been documented in patients with breast cancer. Wasif et al²⁰ surveyed SSO members specializing in breast cancer and found significant variation in approach to MM amongst the different specialties. Surgeons were more likely than MO to view MM as significant but only 23% recommended axillary lymph node dissection despite

consensus guidelines²¹. This is surprising since the role of MM in breast cancer is better established and suggests that intrinsic biases exist among practitioners.

Our aim was to assess the influence of MM disease on treatment decisions for patients with MM disease and Stage II colon cancer. The study identified significant variation in the approach and management of these patients especially when comparing SO and MO. It also demonstrated that while many oncologists feel MM has significant prognostic implications, only few send lymph nodes for routine IHC. The reason for this is unclear but may be due to limitations in staining experience by local pathology departments,²² poor availability of IHC,²³ or may reflect differences between practice and opinion.

There are limitations to this survey since a response rate of 15% may not accurately reflect the views of the respective societies and may introduce bias. Moreover, the survey was only submitted to members of the SSO and ASCO, which may not be reflective of the entire population of MO's and SO's treating patients with Stage II CC. The questions were brief to keep the survey short and as such the survey is not a comprehensive survey of all potential variations in staging and approach to therapy. The questionnaire is an instrument that may limit the ability of the respondent to clarify responses and thus allow bias interpretation of responses related to the case presentation. Nonetheless, the findings suggest that MM plays an influential role in the management of adjuvant therapy and supports data from our collective clinical experience in our prospective randomized multicenter trials.²⁴

Conclusion

This survey suggests that MM disease in stage II CC influences adjuvant treatment decisions absent known prognostic benefit. MM appears to have greater influence amongst MO's and this may reflect different interpretations of the literature or inherent biases present between specialties. Nevertheless, both MO and SO agree that it is crucial to improve our staging and prognostic indicators to improve clinical decision support and to avoid unnecessary toxicity and expense of those patients cured by surgery alone.

Recent molecular studies have clearly demonstrated that stage II colon cancer patients can be stratified into high and low risk groups. While these molecular signatures have not been predictive for the benefit of adjuvant chemotherapy in high risk node-negative groups, ongoing studies will likely determine their predictive value. Furthermore, an international multicenter prospective trial to clarify the role of MM disease and develop a prognostic profile that includes primary tumor and regional nodal gene signatures is underway (NIH# 2RO1CA090848 PI Bilchik). Since this trial includes surgical quality (>12LN's) and pathological ultra-staging (pan-CK IHC on all H&E negative lymph nodes) in the absence of chemotherapy, with minimum 4-year follow-up, a high risk group will be identified, and predictive model and decision support tool trained, tested and cross validated for widespread clinical use. Until completion of this trial we consider the use of adjuvant therapy for Stage II colon cancer with MM, although appealing, purely investigational.

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Abbreviations List

CC	Colon Cancer
MM	Micrometastases
H&E	Hematoxylin and Eosin
IHC	Immunohistochemistry
PCR	Polymerase Chain Reaction
MO	Medical Oncology(ist)
SO	Surgical Oncology(ist)
SSO	Society of Surgical Oncology
ASCO	American Society of Clinical Oncology

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Table 1

Questionnaire to assess the significance of micrometastases in stage II colon cancer.

1	What is your board certification?
a.	Medical Oncology
b.	Surgical Oncology
c.	Pathology
d.	Other
2	Where do you practice?
a.	Northeast
b.	Southeast
c.	Northwest
d.	Southwest
e.	Foreign
3	What is your practice experience?
a.	< 5 years
b.	5 – 10 years
c.	> 10 years
4	What is your practice setting?
a.	Academic
b.	Community
5	Is the number of lymph nodes removed at the time of surgery for colon cancer clinically relevant?
a.	Yes
b.	No
6	Do you regard the presence of micrometastatic disease (identified by immunohistochemistry in hematoxylin and eosin negative nodes) in stage II colon cancer to have prognostic significance?
a.	Yes
b.	No
c.	Not sure
7	Should micrometastatic disease in lymph nodes be included in the AJCC classification?
a.	Yes
b.	No
8	If we included MM disease in the AJCC classification how would you classify it?
a.	N0
b.	N0 – 1
c.	N1
9	In deciding on which patients will need adjuvant chemotherapy for stage II colon cancer; would the presence of micrometastatic disease impact your decision?
a.	Yes
b.	No
10	Are lymph nodes routinely sent for immunohistochemistry at your institution?
a.	Yes
b.	No

Table 2

Demographic characteristics of survey respondents

Characteristics	No. (%)
Specialty	
<i>Medical Oncology</i>	304 (50)
<i>Surgical Oncology</i>	156 (26)
<i>Pathology</i>	115 (19)
<i>Other</i>	27 (5)
Geography	
<i>Northeast</i>	87 (20)
<i>Southeast</i>	81 (19)
<i>Midwest</i>	82 (19)
<i>Southwest</i>	75 (17)
<i>Northwest</i>	17 (4)
<i>Foreign</i>	89 (21)
Practice Experience	
<i>< 5 years</i>	96 (16)
<i>5 to 10 years</i>	142 (24)
<i>> 10 years</i>	364 (60)
Practice Type	
<i>Community</i>	292 (49)
<i>Academic</i>	289 (48)

Table 3

Factors considered in selecting patients to treat with adjuvant chemotherapy.

Response	Offer adjuvant therapy	P Value
MO vs. SO vs. Path	69% vs. 52% vs. 60%	0.002
Community vs. Academic Practice	66% vs. 59%	0.13
Practice in USA vs. Outside USA	63% vs. 60%	0.63
<10 years in practice vs. >10 years	63.1% vs. 62.5%	0.88
# Nodes removed clinically relevant, yes vs. no	62% vs. 65%	0.71
Stage N0 vs. N0-1 vs. N1	23% vs. 53% vs. 91%	<0.001
MM hold prognostic value vs. do not hold prognostic value	85% vs. 19%	<0.001
Perform IHC routinely vs. not performed routinely	73% vs. 61%	0.024

MO, medical oncology; SO, surgical oncology; Path, pathology; MM, micrometastases; IHC, immunohistochemistry.

Table 4

Impact of MM in management of Stage II colon cancer by specialty

Response (Yes)	MO(%)	SO (%)	P value
Offer adjuvant Rx	68.1	50.7	<0.001
MM Should be N1 Stage	52.2	39.9	0.02
AJCC staging to Include MM	73	63.8	0.04
MM prognostic value	53.1	46.7	<0.01

MO, medical oncology; SO, surgical oncology; Rx, treatment; MM, micrometastases; TNM, AJCC staging

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