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Surgical management of metastatic colon cancer: A population-based analysis

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ABSTRACT

Background: Metastasectomy has a curative potential in colon cancer, but its benefits have not been ascertained in population data. Our objective was to evaluate utilization of metastasectomy in colon cancer and its survival outcomes in groups defined by different age at diagnosis, tumor grade or varying extent of nodal spread.

Methods: We extracted data from the Surveillance, Epidemiology and End Results database on adult patients with stage IV colon cancer diagnosed between 2003 and 2011. We analyzed the association of overall survival (OS) with metastasectomy using multivariable Cox models.

Results: Among 41,137 patients with stage IV cancer, 26,607 (65%) underwent primary surgery and 5028 (12.2%) underwent metastasectomy. Older patients were less likely to have ≥ 12 lymph nodes examined in the surgical specimen, but also less likely to have nodal metastases when adequately staged (from 86% for age <50 years to 79% for age ≥ 85 years). Metastasectomy was less common in older patients (from 18% for age <50 years to 7% for age ≥ 85 years). OS after resection was inversely associated with age and nodal involvement. The association of metastasectomy with survival was favorable in all age groups (hazard ratio, HR, 0.68–0.72, $P < 0.0001$), but it was not significant for those ≥ 85 years old (HR, 0.92, $P = 0.23$). It was also favorable regardless of the extent of nodal spread or tumor grade.

Conclusions: Resection of metastatic site is favorably associated with survival in patients up to 85 years of age. Older patients undergoing metastasectomy are more likely to be node-negative when adequately staged.

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1. Introduction

Colorectal cancer is the third leading cause of cancer death in the United States (US) and its incidence increases with age [1]. About 70% of colon cancers occur in patients older than

65 years, and 40% in those older than 75 years. The US Census Bureau projects that the number of Americans older than 65 years old is going to double by 2030. Colon cancer in older patients will thus be a significant problem to address. Few clinical trials evaluated treatment modalities specifically

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indicated for this age group and little is known about differences in therapeutic benefits of various interventions for patients who are young, older and very old.

Although metastatic colon cancer is generally incurable, resection of oligometastatic disease limited to liver or lung has a curative potential for about 20–25% of patients and is endorsed by national guidelines [2–4]. The benefits of metastasectomy have not been evaluated in population-based data, and clinical case series have reported that age is not a significant predictor of survival after colorectal liver metastases resection [5,6]. Regional lymphatic spread is predictive of worse outcome after resection, although it is also not clear whether the benefit of metastasectomy is different for patients with or without nodal involvement [6,7].

The objective of our study was to evaluate the rate of utilization of metastasectomy in the US among patients in different age groups and to investigate heterogeneity of association of the surgery with survival in groups defined by age, sex, tumor grade and extent of nodal involvement.

2. Methods

2.1. Data Source and Cohort Selection

The study used the Surveillance, Epidemiology and End Results (SEER) database curated by the National Cancer Institute. The SEER program collects data on cancer incidence, treatment (with the exception of systemic therapy) and outcomes from 18 population-based registries in the US, currently covering about 28% of the population. We extracted case listings of adult patients with metastatic colon cancer diagnosed between 2004 and 2012, with survival follow-up available until December 31st, 2012 [8]. The study timeframe was selected to coincide with introduction of consistent coding for a surgical procedure to a metastatic site, and

recording of the carcinoembryonic antigen (CEA) level in the database which began in 2004.

We selected cases using topography codes (colon, excluding rectum), year of diagnosis, age at diagnosis 20–99 years, and the following histology codes according to the International Classification of Diseases in Oncology, 3rd edition (ICD-O-3): 8140 (adenocarcinoma, not otherwise specified), 8210 (in adenomatous polyp), 8255 (with mixed subtypes), 8261–8263 (in villous or tubulovillous adenoma), 8480–8481 (mucinous or mucin-producing) and 8490 (signet-ring). Other malignancies such as carcinoid, neuroendocrine, squamous carcinoma, gastrointestinal stromal tumors etc. were excluded because they are biologically distinct and managed using different treatment paradigms. Metastatic disease was defined as stage IV at diagnosis according to the American Joint Commission on Cancer system, and did not include patients experiencing metachronous recurrence of a previous early-stage cancer. We excluded cases diagnosed by death certificate or autopsy and those without recorded survival time ($N = 116$).

2.2. Variables

Race/ethnicity was classified as White non-Hispanic, White Hispanic, Black, or Asian/other. Surgical procedure for the primary tumor site was identified in the database as local excision or as partial/total colectomy. For the purpose of designation of potentially curative resection, only codes for at least partial colectomy were considered. The number of metastatic regional lymph nodes was derived from pathology reports of the resection specimens and classified as N0, N1 (1–3 positive lymph nodes) or N2 (≥ 4 lymph nodes). In order to avoid information bias related to suboptimal locoregional staging, we assigned the nodal status only for patients who underwent colectomy. CEA values in the database were recorded prior to any treatment and categorized as “positive/elevated” or “negative/normal/borderline”, without a specific uniform cutoff.

In accordance with the SEER coding manual, surgical removal of the distant site (metastasectomy) was recorded if it was undertaken as part of the initial treatment course. It was differentiated from resection of contiguous organs, distant lymph nodes or incidental removal of other organs (appendix, gall-bladder etc.) during abdominal surgery. However, the specific site of metastasis (lung, liver, ovary or other) was not differentiated. Patients who had an indication of composite surgery with removal of contiguously involved organ, distant lymph nodes and/or metastatic sites were not analyzed within the metastasectomy group, because it was uncertain whether metastasectomy was actually part of the procedure. As a sensitivity analysis, all calculations were performed including this group as potentially having metastasectomy and no significant differences were observed.

2.3. Statistical Analysis

Patient characteristics in groups were summarized in a tabular form. The relative risk of undergoing metastasectomy was calculated in a multivariable log-binomial model [9]. Exponentiated coefficients from this model directly correspond to risk ratio or relative risk, which is easier to interpret

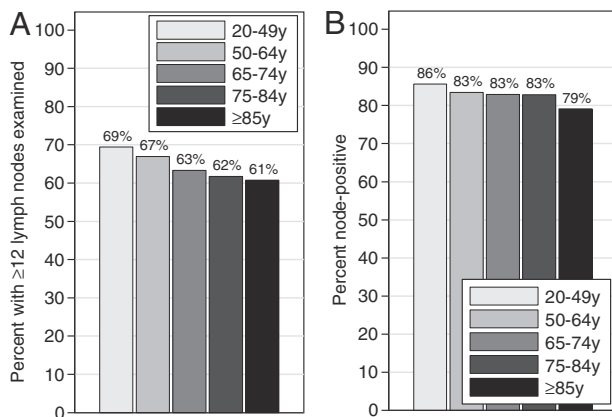


Fig. 1 – (A) Proportion of cases with at least 12 lymph nodes examined in the surgical specimen, among patients with metastatic colon cancer undergoing colectomy, by age group. (B) Proportion of cases with nodal metastases among patients with metastatic colon cancer who underwent resection and had at least 12 lymph nodes examined in the surgical specimen, by age group.

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