Sex-Specific Differences in Colon Cancer when Quality Measures Are Adhered to: Results from International, Prospective, Multicenter Clinical Trials

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BACKGROUND: There is no consensus on the relationship between patient sex and the location, stage, and oncologic outcome of colon cancer (CC). We hypothesized that there is a sex-specific difference in the biology and management of CC.

STUDY DESIGN: Our cohort was drawn from a database of patients enrolled in international trials of nodal ultrastaging for nonmetastatic CC. These trials required strict adherence to surgical and pathologic quality measures. Postoperative follow-up included colonoscopy at 1 and 4 years and annual CT scans. Sex-specific differences in tumor biology, location, stage, and recurrence were evaluated by chi-square, Fischer's exact, and independent *t*-tests.

RESULTS: The cohort included 435 males (median age 69 years) and 423 females (median age 70 years). Females had more right-sided ($p = 0.03$) and earlier T stage ($p = 0.05$) tumors, but there was no sex-based difference in pathologic grade, total lymph nodes retrieved, nodal positivity ($p = 0.47$) or lymphovascular invasion ($p = 0.45$). The overall 4-year disease-free survival (DFS) was comparable in females and males (77.9% and 77.5%, respectively). By multivariate analysis, only nodal positivity and cancer recurrence affected overall survival (OS) ($p = 0.008$). Neither sex nor primary tumor affected DFS or OS.

CONCLUSIONS: This is the first prospective study to demonstrate sex-specific differences in location and T stage of CC when surgical and pathologic management adhered to strict quality standards. The predominance of right-sided CC in females suggests that flexible sigmoidoscopy may be inadequate for screening and surveillance. Interestingly, earlier stage and right-sided location did not confer a DFS or OS advantage for women. Additional studies are needed to determine why females have a higher propensity for right-sided lesions and a potential difference in CC biology. (J Am Coll Surg 2017;225: 85–92. © 2017 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Despite growing awareness for cancer screening and prevention, colon cancer (CC) remains one of the most commonly diagnosed cancers, responsible for more than 600,000 deaths per year globally.[1] Given this high prevalence, along with the vast number of treatment options available, much interest has been devoted to understanding the biology and behavior of CC. With increased attention toward long-term oncologic outcomes, there has been growing controversy on sex-specific outcomes and treatments in colon cancer.[2-5] Several large contemporary studies have suggested that women may present more commonly with right-sided lesions, more advanced tumors, and more aggressive biologic characteristics that confer a poorer oncologic outcome compared with male counterparts, which is in contrast to historical studies.[6-11] Additionally, screening patterns in females are far more inconsistent than in males.[8,12] Most recently, the results of a federally funded prospective trial showed that primary tumor location

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Abbreviations and Acronyms

CC = colon cancer
DFS = disease-free survival
HR = hazard ratio
HRT = hormone replacement therapy
MSI = microsatellite instability
OS = overall survival

conferred survival differences in patients with metastatic colorectal cancer.[13] We hypothesized that patient sex also affects the biology and outcome of CC.

METHODS

Patient selection

Data were retrospectively analyzed from a prospectively accrued cohort enrolled in 2 randomized, multicenter, international clinical trials of ultrastaging in CC.[14,15] Inclusion criteria consisted of those patients older than 18 years of age, with good performance status, and absence of distant metastases on spiral CT with IV and oral contrast of the abdomen and pelvis. This was obtained within 8 weeks of trial enrollment, and all patients required tissue diagnosis via colonoscopy for trial eligibility. Patients with any history of inflammatory bowel disease, a previous malignancy in the 3 years preceding their colon cancer diagnosis, pregnant or potential childbearing females, or those enrolled in another clinical trial were excluded from the study.

Once enrolled, all patients received standardized operative resection with strict adherence to surgical and pathologic quality standards. This included harvesting a minimum of 12 lymph nodes, achieving at least a 5-cm longitudinal surgical margin, and high ligation of the vascular pedicle, with resection of the mesocolic section supplying the segment of interest. Pathologic assessment was performed according to the guidelines set forth by the College of American Pathologists, which included sequential histologic, immunohistochemical, and molecular analyses of at least 12 nodes.[14] Staging was performed according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 6th edition.

To monitor for recurrence, patients were examined every 6 months for the first 2 years, and then yearly thereafter for 48 total months. Their visits included endoscopy at 1 and 4 years, and an annual CT scan. Recurrence was determined based on the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines.

Statistical methods

Statistical analysis was performed using SPSS Statistics software (IBM Corp) and performed by a statistician. A 2-sided p value < 0.05 was considered statistically significant, and chi-square, Fischer's exact test, and independent *t*-test statistics were used to analyze proportions and comparisons. Cancer-specific and overall survival were assessed with Kaplan-Meier and Cox regression analysis, with and without adjustments for relevant biologic characteristics. Patients lost to follow-up were excluded from survival analysis. From the complete Cox regression model, a backward likelihood ratio model was used for assessment by multivariable logistic regression.

RESULTS

Patient characteristics

Of 888 patients available in the database, those without sex information (n = 33) were excluded from any further analysis. As shown in Table 1, male and female patients were of similar ages, but females had a higher proportion of right-sided lesions (p = 0.03). These lesions were more likely to be earlier lesions; women had nearly twice the percentage of T1 lesions than men (p = 0.05). There was no statistically significant difference in the ratio of low, intermediate, and high grade tumors, nor was there a difference in the median number of lymph nodes harvested, the rate of nodal positivity, or the frequency of lymphovascular invasion (Table 1). Distribution across stage after pathologic assessment was not statistically different between groups (p = 0.23). Four-year recurrence rates were lower in females, but this difference was not significant (p = 0.83).

Survival analysis

Overall survival (OS) was 81.6% in females and 83.5% in males (p = 0.75) (Fig. 1). Disease-free survival (DFS) was also not statistically significantly different: 77.9% in females and 77.5% in males (p = 0.76) (Fig. 2). Univariate survival analysis found a significantly increased risk of death for patients with node-positive disease (p < 0.001) and for those who experienced a recurrence (p < 0.001) (Table 2). Patients who had sigmoid tumors demonstrated a statistically significant OS benefit compared with patients with proximal lesions (hazard ratio [HR] 0.38; 95% CI 0.18 to 0.82) (Fig. 3). On sex-specific analysis, females demonstrated a worse survival for right-sided colon cancer compared with sigmoid, but male survival was not statistically different based on location (p = 0.03, p = 0.18, respectively) (Fig. 4). Overall survival was better among patients with T1 vs T4 lesions, but this difference was not significant (HR 0.11; 95% CI 0.01 to 1.05; p = 0.055). At each T stage, there was no significant difference between nodal positivity