Clinical issues in the surgical treatment of colon cancer
Amri, R.

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Chapter 7:

The fate of unscreened women in colon cancer: impact on staging and prognosis

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Liliana G. Bordeianou
Patricia Sylla
David L. Berger

Abstract

Background
Several nationwide reports show lower female participation in colon cancer screening. We therefore assessed for outcome differences in women of screening age presenting for surgical treatment of colon cancer patients.

Methods
All patients over 50 undergoing surgery for first-onset colon cancer at Massachusetts General Hospital (2004-2011) were included. Differences between (unscreened) women and the remaining population in presentation characteristics and subsequent morbidity and mortality were assessed.

Results
We included 919 patients (49.1% female). Women were less often diagnosed through screening (26.4 vs. 32.7%; \( P = 0.036 \)). Unscreened women were at significantly higher risk (all \( P < 0.001 \)) for having high-grade tumors (RR=1.61), lymph node metastasis (RR=1.36) and distant metastasis (RR= 2.26) on pathology, leading to higher colon cancer-related mortality (RR=1.72).

Conclusions
Unscreened women present with more advanced colon cancer and higher mortality, confirming that disparities in screening lead to ever increasing disparities in outcomes.
Colon cancer is the most prevalent malignancy to consistently affect men and women equally.¹ As a result, the US Preventive Services Task Force has recommended screening methods that are independent of sex and based solely on patient age and family history.² The existent screening recommendations have led to a consistent decrease in colon cancer diagnosis rates,³ and also contributed to a significant improvement in outcomes for those whose disease was identified on screening.⁴ Women on average have been shown to fare slightly better after colon cancer diagnosis, with better overall survival⁵ or even better stage-specific outcomes.⁶,⁷ Whether the slight edge in colon cancer outcomes is related to actual cancer-related factors remains debatable, and some authors have provided arguments for alternative explanations, including the confounding effect of comorbidities⁸ or even the longer overall life expectancy of women.⁹

The introduction of large-scale screening programs is changing the makeup of the colon cancer patient population; depending on the compliance rates of both sexes, the relative survival advantage among women may change as well. Outside the United States, some major reports on screening initiatives show that women are more compliant to screening initiatives.¹⁰,¹¹ Conversely, several US nationwide reports have shown an incidence of lower screening compliance rates in women, be it in fecal occult blood tests (FOBT),¹²,¹³ colonoscopies,¹²,¹⁴ or combined screening rates.¹⁵

In this large single-center series, we aim to highlight the extent of these sex differences in screening presentation rates in our population of surgically treated colon cancer patients and to demonstrate their impact on outcomes. As a high-volume urban tertiary care center in a state providing universal health care, a relatively large number of patients with colon cancer are diagnosed through screening; however, this percentage still barely exceeds 20%. This complete cohort of colon cancer patients was used previously to demonstrate the beneficial effect of screening on the baseline staging and outcomes of this screening population.⁴ and was also shown in earlier work to be among those where significant sex disparities, detrimental to women, exist in screening rates.¹⁶

Our hypothesis is that unscreened women, a group of significant size, are faring worse than the remainder of surgical colon cancer patients, and our aim is to measure the magnitude of these differences within the screening age range, in terms of presentation characteristics, surgical stay characteristics, and outcomes.
Methods

Patients and setting

This research was set at Massachusetts General Hospital, a tertiary public hospital where about one fifth of patients operated on for colon cancer are diagnosed through screening methods. In this hospital, all cases of colon cancer treated surgically from January 2004 to December 2011 (n=1071) are included in a prospectively maintained Institutional Review Board-approved retrospective database. Data gathered in this database came from internal admission and follow-up records, operative and pathology reports, as well as the Massachusetts General Hospital cancer registry and the Social Security Death Index for survival data.

The dataset was reviewed to include the primary screening population as a specific subset for this analysis. This was defined as all patients over 50 years of age without a previous history of colorectal cancer. Although current screening guidelines recommend against routine screening above age 75, we chose not to put an upper age limit to the included population as many patients over 75 still undergo primary and secondary screening for pre-existing risk such as history of polyps, and this upper age limit for average-risk screening was only released in 2008, when about half of our patients had already been diagnosed. A screening diagnosis was defined as any colon cancer diagnosis resulting from a screening intervention: these were either a screening colonoscopy (with or without prior history of polyps) or a positive FOBT followed by a colonoscopy to confirm diagnosis.

All the analyses were performed to separately compare unscreened women with 3 other groups: unscreened men, women who were diagnosed through screening, and the totality of the screening population. Where relevant, the subgroups are combined to assess differences between unscreened women and the remainder of the screening population.

Baseline analysis focused on comorbidity, and especially factors associated with colon cancer risk, namely diabetes type inflammatory bowel disease, smoking, and obesity expressed through body mass index (BMI). This was followed by presentation characteristics, including rates of metastatic disease confirmed within 30 days of surgery, preoperative chemotherapy, palliative treatment, emergency admissions, and, for evident reasons, screening diagnoses. Screening diagnosis was expressed as an overall rate, as well as stratified by initial detection through FOBT, or endoscopy with or without surveillance for polyps. Perioperative outcomes were next to be assessed, and include length of stay, length of surgery, need for multivisceral resection, postoperative complication rates, and surgical pathology, including
American Joint Committee on Cancer Tumor, Node, Metastasis (AJCC TNM) classification, tumor grade, and extramural vascular invasion. The last pillar of our analysis consisted of the comparison of long-term outcomes, focusing on recurrence and disease-free survival, as well as overall survival and disease-specific survival.

Statistical analysis

A 2-tailed \( P \)-value of 0.05 or lower was considered statistically significant. All statistical analysis was performed using the SPSS version 20.0 statistical software package (IBM SPSS Statistics for Windows; Armonk, NY: IBM Corp). Comparison between groups for nominal outcomes was performed using a chi-square statistic and a Mann-Whitney U test for continuous outcomes. Multivariate analysis was also performed, using binary logistic regression for dichotomous outcomes and Cox proportional hazards models for continuous time-related outcomes. The multivariate analysis would verify if any significant findings in terms of outcomes are stage independent and still present after correction for potential confounders we may encounter. Kaplan-Meier (log-rank test) and multivariate Cox survival curves were also used to show outcomes over time.

Results

Baseline characteristics

Of 919 patients included for analysis, 451 (49.1\%) were female. As suspected, women presented significantly less often through screening methods (26.4\% vs. 32.7\%, \( P = 0.036 \)). In terms of baseline characteristics, women were significantly older (median age 71 vs. 68 years, \( P = 0.012 \)), while men presented with higher diabetes type 2 rates (22.1\% vs. 15.5\%, \( P = 0.05 \)), a higher mean BMI (28.2 vs. 27.0, \( P < 0.001 \)), and more ever smokers (65.0\% vs. 46.4\%, \( P < 0.001 \)).

Looking specifically at women presenting outside of screening, baseline characteristics relative to nonscreening men reiterated sex differences in BMI and smoking rate differences, in addition to a higher rate of inflammatory bowel disease presentations in nonscreening men (4.4\% vs. 1.2\%, \( P = 0.012 \)). Compared with women presenting through screening, as well as the overall screening population, nonscreening women were older, had higher Charlson comorbidity scores, presented more often in an emergency setting, and presented more often with symptomatic disease (all \( P \leq 0.001 \)). Detailed data on characteristics at presentation are presented in Table 1.
### Table 1. Characteristics at presentation

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Analyzed subsets</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td>P-value</td>
<td>Non-screening female</td>
</tr>
<tr>
<td>n (% included)</td>
<td>451(49.1)</td>
<td>468(50.9)</td>
<td>-</td>
<td>332(36.1)</td>
</tr>
<tr>
<td>Age (median, IQR)</td>
<td>71 (20)</td>
<td>68 (17)</td>
<td>0.012</td>
<td>73 (21)</td>
</tr>
</tbody>
</table>

### Perioperative outcomes

Perioperative characteristics are shown in detail in Table 2. In the general population, women had shorter surgeries (median duration 113 vs. 133 minutes, *P*=0.001), despite having a higher rate of multivisceral resections (16.2 vs. 10.4, *P*=0.006), which correlated with a higher rate of high-grade disease on pathology (23.1% vs. 16.9%, *P*=0.019). Interestingly, nonscreening women also had shorter surgeries than their male nonscreening counterparts (median 118 vs. 136 minutes, *P*=0.021) despite higher rates of multivisceral resections (20.2% vs. 13.7%, *P*=0.027). Potential explanations include the lower mean BMI as well as the difference in central and peripheral fat deposition between men and women. Other perioperative characteristics were not significantly different between nonscreening presentation men and women.

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**Abbreviations:** DM2: type 2 diabetes; FOBT: fecal occult blood test; IBD: inflammatory bowel disease; IQR: interquartile range; SD: standard deviation.

* Versus non-screening women (reference group, highlighted in italics).
Table 2. Perioperative characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Analyzed subsets</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women (n=451)</td>
<td>Men (n=468)</td>
<td>Non-screening female (n=332)</td>
<td>Non-screening male (n=315)</td>
<td>Screening female (n=119)</td>
<td>All screening (n=288)</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery duration (median, IQR; min)</td>
<td>113 (94)</td>
<td>133 (110)</td>
<td>118 (95)</td>
<td>136 (103)</td>
<td>105 (80)</td>
<td>0.057</td>
</tr>
<tr>
<td>Multivisceral resection (%)</td>
<td>16.2%</td>
<td>10.0%</td>
<td>20.2%</td>
<td>13.7%</td>
<td>5.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal metastasis (%N+)</td>
<td>40.5%</td>
<td>38.2%</td>
<td>47.6%</td>
<td>44.1%</td>
<td>21.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Distant metastasis (%M1)</td>
<td>9.5%</td>
<td>6.4%</td>
<td>12.3%</td>
<td>9.2%</td>
<td>1.7%</td>
<td>0.001</td>
</tr>
<tr>
<td>High-grade tumor (%)</td>
<td>23.1%</td>
<td>16.9%</td>
<td>26.1%</td>
<td>20.9%</td>
<td>12.5%</td>
<td>0.007</td>
</tr>
<tr>
<td>EMVI (%)</td>
<td>28.3%</td>
<td>29.7%</td>
<td>34.5%</td>
<td>35.6%</td>
<td>10.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of stay (median, IQR; dy)</td>
<td>5 (4)</td>
<td>5 (5)</td>
<td>5 (4)</td>
<td>5 (6)</td>
<td>3 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Perioperative metastasis (%)</td>
<td>16.0%</td>
<td>15.0%</td>
<td>19.9%</td>
<td>19.0%</td>
<td>5.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>1.8%</td>
<td>1.3%</td>
<td>2.4%</td>
<td>1.9%</td>
<td>0.6%</td>
<td>0.088</td>
</tr>
</tbody>
</table>

EMVI = extramural vascular invasion; IQR = interquartile range.
* Versus non-screening women (reference group, highlighted in italics).

Nonscreened women had significantly higher rates of multivisceral resections, nodal metastasis, high-grade disease, extramural vascular invasion, duration of admission, and perioperative metastasis (all P-values ≤0.01) compared with screening sets of both women only and the overall screening population. In addition, nonscreening women also had a significantly higher perioperative mortality rate when compared with all screened patients (2.4% vs. 0%, P=0.008).

Long-term outcomes

In terms of long-term outcomes, Table 3 shows no statistically significant differences between men and women, although percentage rates indicate slightly worse outcome percentages for women, both in the overall group and the nonscreening subsets for rates of postoperative chemotherapy, overall metastatic disease, all-cause mortality, and colon cancer mortality. Compared with screening diagnosis subsets, differences were significant in terms of postoperative chemotherapy, overall metastatic disease, all-cause mortality, and colon cancer mortality, also leading to significant differences in median durations of survival, disease-free survival, and therefore follow-up duration.
Table 3. Univariate assessment of long-term outcomes

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Analysed subsets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female (n=451)</td>
<td>Male (n=469)</td>
</tr>
<tr>
<td>Postoperative chemotherapy</td>
<td>33.7%</td>
<td>33.3%</td>
</tr>
<tr>
<td>Follow-up duration (M, months)</td>
<td>41 (45)</td>
<td>45.5 (52)</td>
</tr>
<tr>
<td>Survival duration † (M, months)</td>
<td>45 (44)</td>
<td>46 (53)</td>
</tr>
<tr>
<td>Disease-free survival (M, months)</td>
<td>34 (58)</td>
<td>35 (62)</td>
</tr>
<tr>
<td>Metastasis: all cases</td>
<td>26.2%</td>
<td>25.2%</td>
</tr>
<tr>
<td>Metastasis in follow-up</td>
<td>10.2%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Death: all causes</td>
<td>36.8%</td>
<td>34.8%</td>
</tr>
<tr>
<td>Death: colon cancer</td>
<td>21.1%</td>
<td>20.3%</td>
</tr>
</tbody>
</table>

M = median (interquartile range).
* Versus non-screening women (reference group, highlighted in italics).
† Survival duration based on Social Security Death Index data.

Multivariate models

In multivariate analysis (Table 4) adjusting for follow-up, staging, age, and comorbidity where relevant, sex differences remained statistically nonsignificant but with largely unfavorable point estimates for women. Compared with screening presentations, differences in overall metastatic disease and all-cause mortality remained significant after adjustment for follow-up duration, while in Cox regressions, survival duration adjusted for staging, age, and comorbidity and stage-adjusted disease-free survival were no longer significant.

Table 4. Multivariate assessment of long-term outcomes

<table>
<thead>
<tr>
<th>Binary outcomes (logistic regression)</th>
<th>Versus nonscreening men</th>
<th>Versus screening women</th>
<th>Versus screening population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI) (covariates)</td>
<td>P-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>1.05(0.74-1.49) (FU)</td>
<td>0.78</td>
<td>3.11(1.64-5.88) (FU)</td>
</tr>
<tr>
<td>Metastasis in FU</td>
<td>0.99(0.62-1.61) (FU)</td>
<td>1</td>
<td>1.98(0.84-4.55) (FU)</td>
</tr>
<tr>
<td>Death: all causes</td>
<td>1.07(0.76-1.52) (FU/Ch/Age)</td>
<td>0.69</td>
<td>2.30(1.33-3.99) (FU/Ch/Age)</td>
</tr>
<tr>
<td>Death: colon cancer</td>
<td>0.97(0.61-1.53) (FU/St)</td>
<td>0.88</td>
<td>1.32(0.56-3.17) (FU/ St)</td>
</tr>
<tr>
<td>Duration outcomes (Cox regression)</td>
<td>HR (95% CI)</td>
<td>P-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Survival duration</td>
<td>1.12(0.88-1.43) (St/Age/Ch)</td>
<td>0.38</td>
<td>1.43(0.90-2.27) (St/Age/Ch)</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>1.10(0.83-1.44) (Stage)</td>
<td>0.51</td>
<td>1.46(0.81-2.16) (Stage)</td>
</tr>
</tbody>
</table>

Ch: colon cancer-adjusted Charlson comorbidity index; CI: confidence interval; FU: follow-up; HR: hazard ratio (calculated for non-screening women versus respective group); OR: odds ratio; St: AJCC Staging.

Figure 1 showing both univariate Kaplan-Meier survival estimates and the covariate-adjusted Cox proportional hazards survival models show the differences between nonscreening women and the remainder of the screening population, in order to illustrate the
relative magnitude of the detrimental differences in these long-term outcomes, both with and without adjustment for relevant covariates. This shows highly significant univariate differences ($P<0.001$), corresponding to a univariate hazard ratio of 1.49 (95%CI: 1.16-1.93) for shorter disease-free survival and hazard ratio of 1.51 (95%CI: 1.22-1.88) for shorter survival. Multivariate models again show no significant stage-adjusted outcomes.

**Figure 1. Survival curves**

The left panes show the Kaplan-Meier survival curves; the right panes are multivariate Cox proportional hazards survival estimates. Red lines show survival curves for unscreened women, other patients are shown by the blue lines.
Comments

In population-based analysis of screening participation performed in the United States over the last 15 years, a pattern of underrepresentation of women in screening initiatives seems to recur in many instances.\textsuperscript{12-15} We therefore aimed to assess whether women in our patient population were indeed less numerous in their presentation for surgical treatment for colon cancer through screening. If this were the case, our goal would subsequently be to assess whether these women who do not enroll into treatment through screening have more advanced disease and worse long-term outcomes.

Our findings indeed demonstrated that female patients in our cohort were significantly less likely to be diagnosed with colon cancer through screening methods. These patients subsequently presented with more advanced disease, including more metastatic and high-grade disease. In the long term, these women had a nearly 75\% higher cancer-related mortality compared with the remainder of the population. Multivariate assessment of the results shows that the difference in long-term outcomes was indeed largely because of the differences in baseline staging. This demonstrates the beneficial effect of diagnosis through screening, but also illustrates the drawbacks of underscreening: disparities in screening rates lead to disparities in outcomes.

The causal relationship between lower screening rates and worse outcomes is intuitive, and we have already demonstrated the links between screening diagnosis and better long-term outcomes in our population.\textsuperscript{4} It remains, however, unclear why women were less likely to be diagnosed through screening, and the explanation for these differences is outside of the scope of this article and the data available to us, as potential explanations range from behavioral, socioeconomic, and cultural, to gender-specific specificity and sensitivity of testing.

The discrepancy of the findings with earlier data showing better outcomes in colon cancer for women, however, is possibly explained by the effect of age: Earlier reports have already argued that the survival advantage in women may be because of protective effects related to premenopausal hormone levels, with older women actually having worse survival.\textsuperscript{23} This effect may have been cancelled out by our age threshold of 50 years, which partly explains why our findings were conflicting with this premise. At the same time, it also adds gravitas to the importance of accounting for differences in screening presentations and their exacerbating effect in possible sex disparities in older colon cancer patients.
Limitations and implications

The limitations of this study are inherent to its single-center nature. Despite thorough validation of our findings, and a cohort size that allows a high level of statistical confidence for the findings, this remains the finding of a single hospital, with a specific patient population, which is influenced by local demographics and local policy. As a single-center experience, it may or may not be representative of a regional or national issue, although it is certainly a signal that warrants further investigation.

Our findings also present an important case for the continued monitoring of screening disparities, as we show that those left behind clearly form a disadvantaged group that is threatened by more advanced disease and subsequent higher mortality rates. Even if the sex disparities in screening presentations are an isolated phenomenon, there is no reason to believe that the resulting link between underscreening and disadvantageous outcomes is itself localized, especially in light of the high level of statistical certitude encountered in our findings.
References