N0 Stage colon cancer: prognostic role of age in relation to tumor site.

# N0 Stage colon cancer: prognostic role of age in relation to tumor site

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*ABSTRACT. This work investigates the prognostic role of advanced age as a risk factor for recurrence in a population of patients undergoing surgery for N0 stage colon cancer, and also evaluates whether that role is affected by tumor location. A population of 129 consecutive patients who underwent radical surgery for N0 stage colon cancer was selected. Patients were subdivided into three age groups: <65, 65-80 and >80. The only correlation found in the examined population between age and clinical-pathological features was between advanced age (>80) and tumor location in the right side of the colon. Overall survival (OS) and disease-free survival (DFS) were significantly lower in patients over 80 than in the other two classes. Two multivariate analyses were carried out: when tumor location was not considered, age >80 represented a negative prognostic factor for risk of recurrence, regardless of the other factors examined. This role was also confirmed when tumor location was considered. As hypothesized by several authors, the role of advanced age which emerges from this study is mainly due to the increased fragility of elderly patients caused by multiple pathophysiological factors, but it does not necessarily represent an absolute contraindication to surgery. The role played by tumor location remains controversial, as more and more studies show that right colon cancer (RCC) is a biological entity distinct from left colon cancer (LCC). Further studies are required to examine right and left colon cancers as two separate diseases.*

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## INTRODUCTION

Carcinoma of the colon is a multifactorial disease, with complex interactions between genetic and environmental factors, such as other illnesses. It is the most frequent malignant tumor of the gastrointestinal tract and, in absolute terms, is one of the leading causes of morbidity and mortality for cancer. It is also the second leading cause of cancer deaths in the world in both genders.

Population aging is one of the most important demographic phenomena in developed countries, and the incidence of colon cancer has been shown to increase with age (1). That the prognostic role played by age is also linked to the risk of tumor recurrence cannot be excluded.

Recent studies indicate that cancer of the right colon (RCC) is a nosological entity which is distinct from left-sided colon cancer (LCC) (2), as both their biological behavior and clinical features are diversified.

These data led us to analyse the possible correlation between age and tumor location as prognostic factors in the risk of recurrence.

## MATERIALS AND METHODS

One hundred and thirty-nine consecutive patients undergoing radical surgery for N0 stage colon cancer at the Geriatric Surgery Clinic of the University Hospital of Padua between 2002 and 2006 were selected. Patients were subdivided into three age groups: <65, 65-80 and >80.

All patients had check-ups every six months in the first two years after surgery and annually thereafter. Check-ups included clinical examination, serological analysis, imaging (complete abdomen ultrasound, chest X-Ray, CT scan of abdomen) and colonoscopy.

## STATISTICAL ANALYSES

Statistical analyses were performed with Fisher's exact test and the $\chi^2$ test to evaluate the association between categorical variables. Differences between means were calculated with Student's *t*-test. Survival rates were calculated with Kaplan-Meyer curves and differences in survival rates were analysed with the log-rank test. Multivariate survival analyses were performed according to the Cox regression model with dichotomous variables, with standard

*Key words:* Colon cancer, tumor site, elderly patients, prognostic factors.

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Table 1 - *Association between clinico-pathological features and age.*

| Parameters | Numbers (%) | Age | | | *p*-value |
|---|---|---|---|---|---|
| | | <65 (%) | 65-80 (%) | >80 (%) | |
| All | 129 (100) | 25 (19.4) | 63 (41.8) | 41 (31.8) | |
| Gender | | | | | |
| male | 62 (48.1) | 16 (64) | 28 (44.4) | 18 (43.9) | |
| female | 67 (51.9) | 9 (36) | 35 (55.6) | 23 (56.1) | 0.20 |
| Tumor site | | | | | |
| Right Colon | 49 (38) | 6 (24) | 21 (33.3) | 22 (53.7) | |
| Transverse Colon | 3 (2.3) | 0 | 3 (4.8) | 0 | |
| Left Colon | 31 (24) | 9 (36) | 13 (20.6) | 9 (22) | |
| Sigmoid Colon | 46 (35.7) | 10 (40) | 26 (41.2) | 10 (24.4) | **0.04** |
| Histology | | | | | |
| Well differentiated | 29 (22.5) | 7 (28) | 11 (17.5) | 11 (26.8) | |
| Moderately differentiated | 93 (72.1) | 18 (72) | 47 (74.6) | 28 (68.3) | |
| Poorly differentiated | 5 (3.9) | 0 | 4 (6.3) | 1 (2.4) | |
| Mucinous | 2 (1.6) | 0 | 1 (1.6) | 1 (2.4) | 0.63 |
| Depth of tumor invasion | | | | | |
| T1 | 16 (12.4) | 2 (8.0) | 10 (15.9) | 4 (9.8) | |
| T2 | 33 (56.6) | 9 (36) | 13 (20.6) | 11 (26.8) | |
| T3 | 73 (56.6) | 14 (56) | 36 (57.1) | 23 (56.1) | |
| T4 | 7 (5.4) | 0 | 4 (6.4) | 3 (7.3) | 0.58 |
| Peritumoral inflammation | | | | | |
| absent | 11 (8.5) | 2 (8) | 5 (7.9) | 4 (9.8) | |
| present | 118 (91.5) | 23 (92) | 58 (92.1) | 37 (90.2) | 0.94 |
| Vascular invasion | | | | | |
| absent | 80 (62) | 17 (68) | 33 (52.4) | 30 (73.2) | |
| present | 49 (38) | 8 (32) | 30 (47.6) | 11 (26.8) | 0.08 |
| Perineural invasion | | | | | |
| absent | 113 (87.6) | 21 (84) | 58 (92.1) | 34 (82.9) | |
| present | 16 (12.4) | 4 (16) | 5 (7.9) | 7 (17.1) | 0.32 |
| Grading | | | | | |
| G1 | 21 (16.4) | 5 (20) | 6 (9.5) | 10 (27) | |
| G2 | 90 (70.3) | 18 (72) | 48 (76.2) | 24 (60) | |
| G3 | 14 (10.9) | 2 (8) | 8 (12.7) | 4 (13) | 0.31 |



regression to select predictors; outcomes were defined as recurrences, *p*-values of <0.05 were considered statistically significant. All analyses were performed with SPSS (version 18.0, SPSS, Inc., Chicago, IL, USA).

## RESULTS

Sixty-two men (48.1%) and 67 women (51.9%) were studied. Their mean age was 72.9±9.3 years (range 35-96). At the time of surgery, 25 patients (19.4%) were younger than 65, 63 (41.8%) were between 65 and 80, and 41 (31.8%) were over 80. Mean follow-up was 28.3±14.6 months (range 1-60). Recurrence was found in 12 patients (9.3%).

There were 52 (40.3%) patients with RCC and 77 (59.7%) with LCC. Thirteen deaths (10.4%) occurred.

Analysis of clinical pathological characteristics and age (Table 1) indicated that there is a statistically significant association between advanced age (>80) and RCC. No significant association was found between age and histology, tumor grade, peritumoral inflammation, vascular and perineural invasion or stage.

Kaplan-Meier analysis showed that disease-free survival (DFS) was significantly lower in octogenarians (81% at 12 months, compared with 97% in patients of 65-80 years, and 100% in those under 65 years, $p$=0.01) (Fig. 1).

In multivariate analysis (Cox regression), age >80 years was found to be significantly associated with in-

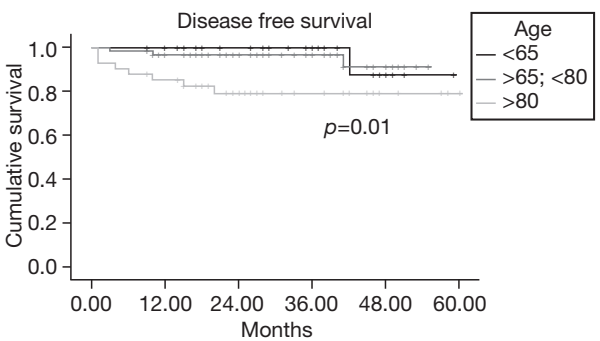


Fig. 1 - *Disease-free survival for population of 129 patients, in three age classes.*

Table 2 - *Multivariate analysis (Cox regression model) of correlation between risk of relapse and clinico-pathological features.*

| | Relapse | | |
|---|---|---|---|
| | **Hazard Ratio** | **95% CI** | ***p*-value** |
| Age (>80) | 4.007 | 1.317-12.191 | **0.014** |
| N° lymph nodes examined (<12) | 1.762 | 0.481-6.453 | 0.392 |
| Gender (male) | 1.692 | 0.511-5.602 | 0.398 |
| Staging (T3-T4) | 1.060 | 0.413-2.719 | 0.904 |
| Grading (G3) | 1.541 | 0.487-4.873 | 0.462 |
| Perineural invasion (present) | 2.078 | 0.246-17.528 | 0.501 |
| Vascular invasion (present) | 2.350 | 0.541-10.209 | 0.254 |
| Peritumoral inflammation (absent) | 1.038 | 0.123-8.772 | 0.973 |

creased risk of relapse (hazard ratio: 4 CI 1.3 to 12.1, $p$=0.01) (Table 2).

When, at a later stage, tumor location was entered into multivariate analysis, age >80 years continued to be a negative prognostic factor, independently of other clinical pathological features (Table 3).

## DISCUSSION

Many studies in the literature have analysed correlations between the clinico-pathologic characteristics of a tumor and patient outcomes (3, 4), but few have evaluated age as a prognostic factor for colon cancer.

After initial evaluation of the data, which revealed that age >80 years is a negative prognostic factor for the risk of tumor recurrence, we examined whether this role was influenced by tumor location.

Advanced age (>80) is associated with a decrease not only in overall survival but also in disease-free survival (DFS). The reduction in DFS in octogenarian patients is explained by the fact that geriatric patients have extreme homeostatic lability, often have chronic polypathologies, and present frequent alterations in pharmacokinetic and pathophysiological responses (5-7).

A statistically significant association was found between advanced age (>80) and location of the tumor in the right side of the colon (Table 2).

A recent meta-analysis (2) recently examined RCC and LCC as two nosological entities distinct from each other, and the former turned out to have worse outcomes than the latter. According to the above study, RCC presents at a more advanced stage and in older patients. This difference is probably due to clinical presentation (non-specific symptoms in RCC compared with LCC) (8, 9), histopathological features, and biological patterns specific to the two tumors. From a molecular point of view, it has been noted that RCCs behave differently from LCCs, the former being associated with higher instability of microsatellites (10), higher incidence of K-ras mutations and increased expression of c-erb B2 and EGF-R (11, 12).

Multivariate analysis of risk of recurrence (Table 3) showed that older age continues to be a negative prognostic factor, independently of tumor location.

## CONCLUSIONS

The data collected during this study demonstrate that advanced age (>80) is a negative prognostic factor for dis-

Table 3 - *Multivariate analysis (Cox regression model) of correlation between risk of relapse and clinico-pathological features, including tumor site.*

| | Recurrences | | |
|---|---|---|---|
| | **Hazard Ratio** | **95% CI** | ***p*-value** |
| Age (>80) | 1.350 | 1.112-13.390 | **0.033** |
| N° lymph nodes examined (<12) | 0.826 | 0.569-9.178 | 0.244 |
| Gender (male) | 0.571 | 0.504-6.209 | 0.373 |
| Staging (T3-T4) | 0.081 | 0.416-2.832 | 0.868 |
| Grading (G3) | 0.278 | 0.420-4.153 | 0.634 |
| Perineural invasion (present) | 0.683 | 0.234-16.780 | 0.531 |
| Vascular invasion (present) | 0.927 | 0.581-10.976 | 0.216 |
| Peritumoral inflammation (absent) | 0.219 | 0.132-11.771 | 0.848 |
| Site (right colon) | 0.467 | 0.156-16.332 | 0.695 |

ease-free survival in patients with stage N0 colon cancer. This role is attributed to the comorbidities which old age brings (2), but may also be linked to other microbiological hypotheses such as remodeling of the immune system (13, 14) and homeostatic responses (2, 3).

The fact that tumor site does not adversely affect the risk of recurrence contrasts with the findings of a meta-analysis by Benedix et al. (2) in which RCC predominantly has a worse prognosis than LCC in elderly patients.

Although this result may be due to the small number of subjects studied, the age factor may really be independent of tumor location as a negative prognostic factor for risk of recurrence.

*Disclosure statement*

The authors have nothing to disclose.

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