**Name of Journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 31323**

**Manuscript Type: ORIGINAL ARTICLE**

***Retrospective Cohort Study***

**Octogenarian patients with colorectal cancer: Characterizing an emerging clinical entity**

Goldvaser H *et al*. Colorectal cancer in octogenarians

Hadar Goldvaser, Noa Katz Shroitman, Irit Ben-Aharon, Ofer Purim, Yulia Kundel, Daniel Shepshelovich, Tzippy Shochat, Aaron Sulkes, Baruch Brenner

**Hadar Goldvaser, Irit Ben-Aharon, Ofer Purim, Yulia Kundel, Aaron Sulkes, Baruch Brenner,** Institute of Oncology, Davidoff Cancer Center, Beilinson Hospital, Rabin Medical Center, Petach Tikva 4941492, Israel

**Hadar Goldvaser, Noa Katz Shroitman, Irit Ben-Aharon, Ofer Purim, Yulia Kundel, Daniel Shepshelovich, Aaron Sulkes, Baruch Brenner,** Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv 64239, Israel

**Hadar Goldvaser,** Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre and the Department of Medicine, University of Toronto, Toronto M5G 0A4, Canada

**Daniel Shepshelovich,** Department of Medicine A, Beilinson Hospital, Rabin Medical Center, Petach Tikva 4941492, Israel

**Tzippy Shochat**, Statistical Consulting Unit, Beilinson Hospital, Rabin Medical Center, Petach Tikva 4941492, Israel

**Author contributions:** Goldvaser H and Brenner B contributed to study conception and design of the study; Goldvasr H, Katz Shroitman N, Ben-Aharon I, Purim O, Kumdel Y contributed to data acquisition; Goldvaser H, Shespshelovich D, Shochat T, Sulkes A, Brenner B contribued to analysis and interpretation of data; Goldvaser H, Katz Shroitman N and Brenner drafted the article; Ben-Aharon I, Purim O, Kumdel Y, Shespshelovich D, Shochat T, Sulkes A made critical revisions related to important intellectual content of the manuscript; Goldvasr H, Katz Shroitman N, Ben-Aharon I, Purim O, Kumdel Y, Shespshelovich D, Shochat T, Sulkes A, Brenner B approved the version of the article to be published.

**Institutional review board statement:** The study was reviewed and approved by our institutional review board (No. of approval RMC 0644-13).

**Informed consent statement:** As this was a retrospective study, informed consent was not required.

**Conflict-of-interest statement:** All the Authors have no conflict of interest related to the manuscript.

**Data sharing statement:** The original anonymous dataset is available on request from the corresponding author at [hadar7g@gmail.com](mailto:hadar7g@gmail.com).

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Correspondence to:** **Hadar Goldvaser, MD,** Davidoff Cancer Center, Beilinson Hospital, Rabin Medical Center, 39 Jabotinski Street, Petach Tikva 4941492, Israel. hadar7g@gmail.com

**Telephone:** +972-3-9789742-1

**Fax:** +972-3-9377902

**Received:** November 10, 2016

**Peer-review started:** November 10, 2016

**First decision:** December 19, 2016

**Revised:** December 26, 2016

**Accepted:** January 11, 2017

**Article in press:**

**Published online:**

**Abstract**

***Aim***

To characterize colorectal cancer (CRC) in octogenarians as compared with younger patients.

***Methods***

A single-center, retrospective cohort study which included patients diagnosed with CRC at the age of 80 years or older between 2008-2013. A control group included consecutive patients younger than 80 years diagnosed with CRC during the same period. Clinicopathological characteristics, treatment and outcome were compared between the groups. Fisher's exact test was used for dichotomous variables and Chi-square was used for variables with more than two categories. Overall survival was assessed by Kaplan-Meier survival analysis, with the log-rank test. Cancer specific survival and disease-free survival were assessed by the Cox proportional hazards model, with the Fine and Gray correction for non-cancer death as a competing risk.

***Results***

The study included 350 patients, 175 patients in each group. Median follow-up was 40.2 mo (range 1.8-97.5). Several significant differences were noted. Octogenarians had a higher proportion of Ashkenazi ethnicity (64.8% *vs* 47.9%, *p <* 0.001), a higher rate of personal history of other malignancies (22.4% *vs* 13.7%, *p =* 0.035) and lower rates of family history of any cancer (36.6% *vs* 64.6%, *p <* 0.001) and family history of CRC (14.4% *vs* 27.3%, *p =* 0.006). CRC diagnosis by screening was less frequent in octogenarians (5.7% *vs* 20%, *p <* 0.001) and presentation with performance status of 0-1 was less common in octogenarians (71% *vs* 93.9%, *p <* 0.001). Octogenarians were more likely to have tumors located in the right colon (45.7% *vs* 34.3%, *p =* 0.029) and had a lower prevalence of well differentiated histology (10.4% *vs* 19.3%, *p =* 0.025). They received less treatment and treatment was less aggressive, both in patients with metastatic and non-metastatic disease, regardless of performance status. Their 5-year cancer specific survival was worse (63.4% *vs*77.6%, *p =* 0.009), both for metastatic (21% *vs* 43%, *p =* 0.03) and for non-metastatic disease (76% *vs* 88%, *p =* 0.028).

***Conclusion***

Octogenarians presented with several distinct characteristics and had worse outcome. Further research is warranted to better define this growing population.

**Key words:** Colon; Rectum; Elderly; Octogenarian; Age

**© The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Data regarding octogenarians with colorectal cancer (CRC) are scarce. We compared octogenarians with CRC to younger patients. Octogenarians had a predominance of Ashkenazi ethnicity, a higher rate of personal history of other malignancies and a lower rate of family history of any cancer or of CRC. Their performance status at presentation was worse and their tumors were more likely to be located in the right colon and to have a poorer differentiation. Octogenarians received less treatment and treatment was less aggressive, regardless of performance status. This might contribute to the worse outcome which was found among the octogenarians.

Goldvaser H, Katz ShroitmanN, Ben-Aharon I, Purim O, Kundel Y, Shepshelovich D, Shochat T, Sulkes A, Brenner B. Octogenarian patients with colorectal cancer: Characterizing an emerging clinical entity. *World J Gastroenterol* 2017; In press

**INTRODUCTION**

Colorectal cancer (CRC) is the fourth most common cancer and the third leading cause of cancer death globally[1]. CRC carries an approximately 4.4% lifetime risk and accounts for 8% of all new cancer cases[2]. It is classified according to local invasion depth (T stage), lymph node involvement (N stage), and presence of distant metastases (M stage). These classification are combined into an overall stage scoring from 1 to 4[3], which provides the basis for therapeutic decisions and prognosis[1].

CRC is predominantly associated with the elderly, with an increasing incidence with age. The median age for CRC diagnosis is 68 years, with about 35% of the patients diagnosed above the age of 75 years[2]. Since the elderly population in Western countries constantly grows, the incidence of CRC in octogenarians is expected to increase in the coming years[4]. Clearly, octogenarians are becoming a substantial population among CRC patients.

Currently, the impact of older age on tumor biology and outcome remains unclear. While some studies imply that elderly patients with CRC might have unique features[5-7] as well as worse outcome[7-9], these findings are not consistent[10-13].

Elderly patients are considerably underrepresented in clinical trials[14,15]. Hutchins et al. reported that CRC patients who were older than 65 and 70 years accounted for only 40% and 14% of patients in clinical trials, respectively[15]. Furthermore, the cut-off for "elderly" patients with CRC in not consistent across different studies, starting from 65 years of age. Studies evaluating octogenarians are scarce[5,6,16]. At present, as octogenarians are rarely included in clinical trials, their optimal management is not clearly defined.

The aim of this study was therefore to better define this growing entity of elderly patients with CRC. As the median age at diagnosis of CRC is 68[2], similar to some recent studies[5,6,16] we chose a cut-off of 80 years old in order to emphasize age-related characteristics.

**MATERIALS AND METHODS**

This was a retrospective, single center cohort study. The study population included all patients who were 80 years old or older at diagnosis of CRC during the years 2008-2013 and were treated at our institute, a large academic tertiary medical center. This group was matched by year of diagnosis with a control group of consecutive patients younger than 80 years at diagnosis. We assumed this population to be representative of the average CRC population.

The medical records of all patients were reviewed and detailed data on patient demographics, risk factors for CRC, clinical-pathological parameters, treatment, adverse events and outcome were retrieved. Patients' performance status (PS) at presentation was determined according to the Eastern Cooperative Oncology Group (ECOG) scale. Staging was defined according to the American Joint Committee on Cancer Staging (AJCC), 7th edition[3]. Grade of toxicity was determined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0[17]. The study protocol was approved by the institutional ethics committee.

***Statistical analysis***

The statistical analysis was generated using SAS software, version 9.4. Fisher's exact test was used for dichotomous variables and Chi-square was used for variables with more than two categories. Overall survival (OS) was assessed by Kaplan-Meier survival analysis, with the log-rank test. Cancer specific survival (CSS) and disease-free survival (DFS) were assessed by the Cox proportional hazards model, with the Fine and Gray correction for non-cancer death as a competing risk. Cox proportional hazard models were also applied for multivariate analysis and hazard ratios estimations. Two-sided p-values less than 0.05 were considered statistically significant.

**RESULTS**

***Patient characteristics***

Three hundred fifty patients with CRC were included in the study, 175 patients in each group. The clinical characteristics of the two groups are detailed in Table 1. Several significant differences were noted. There were more Ashkenazi Jews (64.8% *vs* 47.9%) in the octogenarians group and less Arab patients (0% *vs* 7.1%) or other (1.7% *vs* 8.3%) ethnicities (*p <* 0.001). Octogenarians had a higher incidence of second malignancies (22.4% *vs* 13.7%, *p =* 0.035) but had lower rates of family history of any cancer (36.3% *vs* 64.6%, *p <* 0.001) or CRC (14.4% *vs* 27.3% *p =* 0.006). Smoking was less prevalent in octogenarians (24.6% *vs* 44.3%, *p <* 0.001), while the incidence of other risk factors, including inflammatory bowel disease, history of polyps and familial CRC syndromes, were comparable between both groups.

As expected, there was a remarkable difference in CRC diagnosis following screening, with only 5.7% octogenarians diagnosed by screening compared to 20% in the control group (*p <* 0.001). In addition, octogenarians were less likely to have a PS of 0 or 1 at presentation (71% *vs* 93.9%, *p <* 0.001).

***Tumor characteristics***

Tumor characteristics are depicted in Table 2. Primary tumor location differed between the groups: tumors were located in the right colon in 45.7% of the octogenarians, compared with 34.3% patients in the control group (*p =* 0.029). At presentation, octogenarians had a higher perforation rate (5.7% *vs* 1.1%, *p =* 0.019), while obstruction rates were similar.

Well differentiated histology (grade 1) was less prevalent in octogenarians (10.4% *vs* 19.4%, *p =* 0.025), while other histological characteristics, as well as tumor stage at presentation, were comparable between the groups. With limited genomic data, no apparent differences in RAS and BRAF mutation status were noted. Octogenarians were more likely to have MSI-H (Microsatellite instability- high) status (*p =* 0.001), but such information was available for only 24 (6.9%) patients.

***Treatment***

Significant differences were identified in treatment approach (Table 3). Octogenarians with non-metastatic disease were less likely to receive adjuvant or neoadjuvant treatment (27.5% *vs* 60.9%, *p <* 0.0001). Even a subset analysis for patients with PS 0-1 demonstrated a lower use of adjuvant/neoadjuvant treatment: 32.6% compared to 61.7% (*p <* 0.0001). Of all patients treated with chemotherapy, the percentage of octogenarians treated with oxaliplatin-based regimes was also lower compared with younger patients (29.7% *vs* 59.5%, *p =* 0.002).

Octogenarians with metastatic disease were treated with fewer chemotherapy lines: 34.6% did not receive any treatment, 42.3% received one line and 23.1% received at least two lines, compared with 8.8%, 38.2% and 53%, respectively, in the control group (*p =* 0.016). This difference persisted for patients with metastatic disease with PS 0-1: 23.5% octogenarians did not receive any chemotherapy compared to only 7.7% in the control group (*p =* 0.045). Moreover, octogenarians with metastatic disease underwent local treatment to metastatic sites (including surgery, chemoembolization, stereotactic body irradiation and radiofrequency ablation) less frequently (9.7% *vs* 65.5%, *p <* 0.0001).

Chemotherapy in both the adjuvant setting and in patients with metastatic disease had comparable rates of grade 3-5 hematologic and non-hematologic adverse events (Table 3).

***Outcome***

The median follow-up time was 40.2 months (range 1.8-97.5 mo). During this period, 120 patients died of CRC and 230 remained alive or died of other causes. Octogenarians achieved a status of no evidence of disease (NED) less frequently: 88.8% patients with non-metastatic disease and 5.9% of those with metastatic disease achieved NED, compared to 97.8% and 38.9% in the younger patient group (*p =* 0.003 and *p =* 0.001, non-metastatic and metastatic disease, respectively).

Among patients with non-metastatic disease 5-year DFS rates were 68.7% for octogenarians and 78.7% for younger patients, without reaching statistical significance (*p =* 0.154). The 5-year OS and CSS rates were worse for octogenarians (5-year OS: 38.5% *vs* 74.8%, *p <* 0.0001, 5-year CSS: 63.4% *vs* 77.6%, *p =* 0.009) (Figures 1, 2). Octogenarians had a lower 5-year CSS rate even when the analysis was limited to patients with non-metastatic disease: 76% *vs* 88% (HR = 2.23, 95%CI: 1.09-4.58, *p =* 0.028). However, patients with non-metastatic disease who received adjuvant or neoadjuvant treatment had comparable 5-year CSS rates (80% *vs* 88% for the octogenarians and the control group respectively, *p =* 0.327). Octogenarians with metastatic disease had a worse 5-year CSS rate: 21% *vs* 43% (HR = 1.86, 95%CI: 1.06-3.25, *p =* 0.03).

Most "classical" CRC prognostic factors were found to correlate with CSS and DFS on univariate analysis, including T, N, TNM stage, histological subtype of signet ring cell carcinoma, and presentation with obstruction (Table 4). Diagnosis through screening, perforation, PS 0-1 at presentation and grade were associated with CSS, but not DFS. In addition, family history of CRC was associated with better DFS and CSS rates. Patients with metastatic disease who underwent local treatment to metastatic sites also had a better CSS. We performed multivariate analysis for DFS and CSS including age, gender and variables which were found significant in the univariate analysis. TNM stage, histology, family history of CRC and presentation with perforation retained statistical significance on multivariate analysis for CSS (Table 4). TNM stage, histology, family history of CRC and presentation with obstruction were associated with DFS on multivariate analysis. Age was not associated with neither CSS nor with DFS on these multivariate analyses.

**DISCUSSION**

While the burden of elderly patients with CRC is increasing[2,4], current literature regarding characteristics and optimal management of this subpopulation is unclear. Data are even more limited on the very elderly patients, octogenarians with CRC. In this study, we elected a cut-off of 80 for several reasons. First, the growing number of octogenarians emphasizes the need to explore this population. Second, the cut-off for elderly patients in current literature is inconsistent, starting from 65 years of age, which is clearly not well representative of the nowadays elderly population. Lastly, using a relatively high cut-off may better emphasize the differentiation between the two populations and may elucidate age-dependent differences that might have been masked using a lower cut-off.

In this study, we found a variety of significant differences between octogenarians with CRC and younger patients ("average" patients). Octogenarians had a predominance of Ashkenazi ethnicity, a higher rate of personal history of other malignancies and a lower rate of family history of any cancer or of CRC. In addition, they were less frequently diagnosed by screening; their PS at presentation was worse and their tumors likely to be located in the right colon and to have a poorer differentiation. Moreover, they received less treatment and treatment was less aggressive, both for metastatic and non-metastatic disease, regardless of PS. Not surprisingly, their CSS was worse, both for metastatic and for non-metastatic disease. Some of these findings were described before, and some are novel.

In contrast to other studies[5,6], CRC among octogenarians had no female predominance. The ethnic composition was considerably different between the two groups. There were no Arabs in the octogenarians group as opposed to 7.1% in the control group. This finding is consistent with previous studies which reported a high proportion of Arabs in the young CRC population in Israel[18-20]. The reason for the higher prevalence of Ashkenazi Jews in the elderly group is unclear, although it may at least in part reflect the ethnic distribution in Israel in this age group[21].

Younger patients had a higher prevalence of family history of CRC, a well-established risk factor. In addition, a higher rate of family history of other malignancies in the younger population might represent the presence of other risk factors (for example a family history of endometrial cancer) or even undiagnosed actual cancer-related syndromes. Our finding of better outcome in patients with family history of CRC might be related to better adherence to screening or higher incidence of MMR (mismatch repair) deficiency, which are both associated with better outcome[22-24]. Octogenarians had a higher incidence of secondary malignancies, probably reflecting the increasing incidence of malignancies in the older population[2]. Indeed, most of the other cancer identified in our older group represented other common non-CRC cancers.

As expected, the screening rate was considerably lower among the octogenarians with only 5.7% diagnosed by screening in this group. The higher perforation rate in this population might be related to a lower screening rate. Although the current United States Preventive Services Task Force recommends against routine screening for average risk individuals older than 75[22], current literature regarding the optimal age to discontinue screening is unclear, and it seems that at least some patients might benefit form screening after this age[23,25]. Our findings of low screening rate and worse CSS in octogenarians might further support the need to consider screening for CRC in the elderly, taking into account their life expectancy and comorbidities.

In agreement with previous reports[5-7], we found that octogenarians had clear predilection for right colon tumors. This finding might suggest a distinct pathogenesis of CRC among older patients, such as a higher rate of MMR deficiency or its phenotype, MSI-H tumors. Indeed, we noted, for the first time, that octogenarians had a significantly higher rate of MSI-H tumors. However, as data regarding MSI status were scarce, conclusions from this specific analysis are limited. Since patients with MMR deficiency might benefit from immune check point blockade[26], a routine evaluation of MSI-H status in elderly patients should be considered.

Similarly to earlier studies[16,27,28],octogenarians in the current study were less likely to receive treatment and treatment was less aggressive, both for metastatic and non-metastatic disease. This difference remained statistically significant after adjusting for PS. We could not determine the reason for this finding due to the retrospective nature of this study. As the benefit of both surgery and chemotherapy are well established in CRC[29,30], the worse CSS in the octogenarians in our cohort might be related to the demonstrated avoidance of treatment. Comparable CSS in patients who received adjuvant or neoadjuvant treatment further supports this postulation. Current literature regarding treatment decisions for elderly patients with CRC is conflicting. Alongside reports on the benefit of chemotherapy and surgery in elderly CRC patients[31-38], there are data implying a minimal benefit for oxaliplatin in the adjuvant setting[27,39] and a higher treatment complication rate[28,40] in older patients. In this cohort, there was no difference in chemotherapy associated toxicity. These findings bolster the need for prospective trials aiming to establish the optimal treatment for octogenarians.

Consistent with earlier studies[7-9], octogenarians in our cohort had worse outcome. Nonetheless, as other studies have indicated similar outcomes across different age groups[10-13], the actual impact of age on the outcome of the disease still remains to be established.

Limitations of this study include the retrospective methodology that may cause bias due to unknown or unrecorded confounders. As this is a single center study, it is more vulnerable to such bias. In addition, patients with CRC treated at our tertiary center might not represent the average population with CRC. An additional possible limitation might be a selection bias. Octogenarians included in our study were those referred to an oncologist. Therefore, our cohort might represent more "fit" octogenarians, as other frail octogenarians might have been undiagnosed or were not referred to an oncologist due to their poor clinical status. Nonetheless, the octogenarians in this cohort, who were potentially more "fit" than the average ones, were considerably under-treated compared with younger patients, thus bolstering the validity of this observation. Moreover, data regarding dose reductions were not documented. Therefore, although toxicity rates were comparable between both groups, prospective randomized trials are needed to determine whether toxicity in the older and younger populations is indeed similar. Last, as octogenarians were more likely to have comorbidities and their life expectancy is shorter, conclusions that can be drawn from the difference in survival are limited. However, the difference in CSS was also substantial, implying that octogenarians may indeed have worse outcome.

This study has several strengths. First, it includes a relatively large patient cohort, with a highly representative control group. We found correlations between outcome and most known prognostic factors of CRC, adding to the reliability and validity of the results. Second, as opposed to some large registry-based studies, which might lack important data, we extracted very detailed clinical data from the patients' individual medical files. Third, in contrast to other studies evaluating elderly patients with CRC which included much lower age cut-off[9,10,12,13,19,27,34,38], this study’s cut-off probably might highlighted the differences between older and the younger population better.

Our study indicates that octogenarians with CRC display several differences in clinical and tumor characteristics, supporting the hypothesis of a unique clinical entity in this population, possibly with a distinct pathogenesis. They were less likely to receive treatment despite adequate PS and their outcome was worse. In light of these findings tailoring the management of octogenarians according to their PS and comorbidities should be further studied. Further research is warranted to better clarify the role of screening for the aging population and to determine well defined treatment guidelines for octogenarians with CRC.

**ACKNOWLEDGMENTS**

The authors would like to thank Dr. Eitan Amir and Dr. Daliah Galinsky-Tsoref, for their critical contribution of revising this article. Their involvement improved significantly the quality of our manuscript.

**comments**

***Background***

colorectal cancer (CRC) is predominantly a disease of the elderly. The incidence of octogenarians with CRC is expected to increase in the coming years. Some studies imply that elderly patients with CRC might represent a unique entity and has worse outcome, but data are not consistent. Although the benefit of chemotherapy and surgery in CRC are well establish, elderly patients often receive less treatment. Octogenarians are becoming a substantial population among CRC patients; but they are rarely included in clinical trials. The authors believe more research is desired to better understand the characteristics and the appropriate management of these patients.

***Research frontiers***

The definition of elderly patients with CRC is inconsistent; some studies used relatively low age cut-off. The authors believe focusing on octogenarians enabled better characterization of the elderly population with CRC and highlighted the differences between elderly patients with CRC compared to the average CRC population. In contrast to registry-based studies, we performed a detailed chart review and extracted data regarding various characteristics, as well as treatment and chemotherapy related adverse events. We found correlation between most known prognostic factors for CRC and outcome, which further supports the validity of this study.

***Innovations and breakthrough***

The clinical and pathological differences between octogenarian and the control group suggest CRC in octogenarians might represent a unique clinical entity. Octogenarians were less likely to receive treatment; even if they had good performance status (PS). Chemotherapy treatment was associated with comparable severe adverse events rates. Remarkable worse overall survival (OS) and cancer specific survival (CSS) might imply that avoidance form treatment could contribute to these results.

***Applications***

Older age by itself should not be a contra-indication for oncological treatment. Lack of difference in severe adverse event rates further supports this postulation. In addition, as life expectancy is increasing, screening in fit older population should be considered.

***Peer-review***

The matter studied in the manuscript is important and needed. The overall structure of the manuscript is clear and complete. The language and methods are appropriate.

**REFERENCES**

1 **Brenner H**, Kloor M, Pox CP. Colorectal cancer. *Lancet* 2014; **383**: 1490-1502 [PMID: 24225001 DOI: 10.1016/S0140-6736(13)61649-9]

2 Surveillance Epidemiology and End Results (SEER). Fast Stats. Available from: URL: http: //www.seer.cancer.gov

3 **Edge SB,** Byrd DR, Compton CC. AJCC Cancer Staging Manual, 7th edition. Chicago, Springer, 2010

4 **Christensen K**, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. *Lancet* 2009; **374**: 1196-1208 [PMID: 19801098 DOI: 10.1016/S0140-6736(09)61460-4]

5 **Kotake K**, Asano M, Ozawa H, Kobayashi H, Sugihara K. Tumour characteristics, treatment patterns and survival of patients aged 80 years or older with colorectal cancer. *Colorectal Dis* 2015; **17**: 205-215 [PMID: 25376705 DOI: 10.1111/codi.12826]

6 **Patel SS**, Nelson R, Sanchez J, Lee W, Uyeno L, Garcia-Aguilar J, Hurria A, Kim J. Elderly patients with colon cancer have unique tumor characteristics and poor survival. *Cancer* 2013; **119**: 739-747 [PMID: 23011893 DOI: 10.1002/cncr.27753]

7 **Holt PR**, Kozuch P, Mewar S. Colon cancer and the elderly: from screening to treatment in management of GI disease in the elderly. *Best Pract Res Clin Gastroenterol* 2009; **23**: 889-907 [PMID: 19942166 DOI: 10.1016/j.bpg.2009.10.010]

8 **Dekker JW**, van den Broek CB, Bastiaannet E, van de Geest LG, Tollenaar RA, Liefers GJ. Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. *Ann Surg Oncol* 2011; **18**: 1533-1539 [PMID: 21445672 DOI: 10.1245/s10434-011-1671-x]

9 **Waldron RP**, Donovan IA, Drumm J, Mottram SN, Tedman S. Emergency presentation and mortality from colorectal cancer in the elderly. *Br J Surg* 1986; **73**: 214-216 [PMID: 3947921 DOI: 10.1002/bjs.1800730320]

10 **Mulcahy HE**, Patchett SE, Daly L, O'Donoghue DP. Prognosis of elderly patients with large bowel cancer. *Br J Surg* 1994; **81**: 736-738 [PMID: 8044567 DOI: 10.1002/bjs.1800810540]

11 **Fukuchi M**, Ishibashi K, Tajima Y, Okada N, Yokoyama M, Chika N, Hatano S, Matsuzawa T, Kumamoto K, Kumagai Y, Baba H, Mochiki E, Ishida H. Oxaliplatin-based chemotherapy in patients aged 75 years or older with metastatic colorectal cancer. *Anticancer Res* 2013; **33**: 4627-4630 [PMID: 24123040]

12 **Berretta M**, Aprile G, Nasti G, Urbani M, Bearz A, Lutrino S, Foltran L, Ferrari L, Talamini R, Fiorica F, Lleshi A, Canzonieri V, Lestuzzi C, Borsatti E, Fisichella R, Tirelli U. Oxaliplapin and capecitabine (XELOX) based chemotherapy in the treatment of metastatic colorectal cancer: the right choice in elderly patients. *Anticancer Agents Med Chem* 2013; **13**: 1344-1353 [PMID: 24102280 DOI: 10.2174/18715206113136660347]

13 **Grande C**, Quintero G, Candamio S, París Bouzas L, Villanueva MJ, Campos B, Gallardo E, Alvarez E, Casal J, Mel JR; Grupo Gallego de Investigaciones Oncológicas (GGIO). Biweekly XELOX (capecitabine and oxaliplatin) as first-line treatment in elderly patients with metastatic colorectal cancer. *J Geriatr Oncol* 2013; **4**: 114-121 [PMID: 24071536 DOI: 10.1016/j.jgo.2013.01.001]

14 **Kim JH**. Chemotherapy for colorectal cancer in the elderly. *World J Gastroenterol* 2015; **21**: 5158-5166 [PMID: 25954089 DOI: 10.3748/wjg.v21.i17.5158]

15 **Hutchins LF**, Unger JM, Crowley JJ, Coltman CA, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999; **341**: 2061-2067 [PMID: 10615079 DOI: 10.1056/NEJM199912303412706]

16 **Kumar R**, Jain K, Beeke C, Price TJ, Townsend AR, Padbury R, Roder D, Young GP, Richards A, Karapetis CS. A population-based study of metastatic colorectal cancer in individuals aged ≥ 80 years: findings from the South Australian Clinical Registry for Metastatic Colorectal Cancer. *Cancer* 2013; **119**: 722-728 [PMID: 22990939 DOI: 10.1002/cncr.27802]

17 Common Terminology Criteria for Adverse Events v3.0 (CTCAE) Publish Date: August 9, 2006. Available from: URL: http: //ctep.cancer.gov/protocolDevelopment/electronic\_applications/docs/ctcaev3.pdf

18 **Neufeld D**, Shpitz B, Bugaev N, Grankin M, Bernheim J, Klein E, Ziv Y. Young-age onset of colorectal cancer in Israel. *Tech Coloproctol* 2009; **13**: 201-204 [PMID: 19609485 DOI: 10.1007/s10151-009-0501-7]

19 **Shemesh-Bar L**, Kundel Y, Idelevich E, Sulkes J, Sulkes A, Brenner B. Colorectal cancer in young patients in Israel: a distinct clinicopathological entity? *World J Surg* 2010; **34**: 2701-2709 [PMID: 20809152 DOI: 10.1007/s00268-010-0748-1]

20 **Goldvaser H**, Purim O, Kundel Y, Shepshelovich D, Shochat T, Shemesh-Bar L, Sulkes A, Brenner B. Colorectal cancer in young patients: is it a distinct clinical entity? *Int J Clin Oncol* 2016; **21**: 684-695 [PMID: 26820719 DOI: 10.1007/s10147-015-0935-z]

21 Central Bureau of Statistics. Available from: URL: http: //www.cbs.gov.il/shnaton66/st02\_06x.pdf

22 US Preventive Services Task Force recommendation statement- colorectal cancer screening. Avilable from: URL: http: //www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/colorectal-cancer-screening

23 **van Hees F**, Saini SD, Lansdorp-Vogelaar I, Vijan S, Meester RG, de Koning HJ, Zauber AG, van Ballegooijen M. Personalizing colonoscopy screening for elderly individuals based on screening history, cancer risk, and comorbidity status could increase cost effectiveness. *Gastroenterology* 2015; **149**: 1425-1437 [PMID: 26253304 DOI: 10.1053/j.gastro.2015.07.042]

24 **Samowitz WS**, Curtin K, Ma KN, Schaffer D, Coleman LW, Leppert M, Slattery ML. Microsatellite instability in sporadic colon cancer is associated with an improved prognosis at the population level. *Cancer Epidemiol Biomarkers Prev* 2001; **10**: 917-923 [PMID: 11535541]

25 **Saini SD**, Vijan S, Schoenfeld P, Powell AA, Moser S, Kerr EA. Role of quality measurement in inappropriate use of screening for colorectal cancer: retrospective cohort study. *BMJ* 2014; **348**: g1247 [PMID: 24574474 DOI: 10.1136/bmj.g1247]

26 **Le DT**, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Duffy SM, Goldberg RM, de la Chapelle A, Koshiji M, Bhaijee F, Huebner T, Hruban RH, Wood LD, Cuka N, Pardoll DM, Papadopoulos N, Kinzler KW, Zhou S, Cornish TC, Taube JM, Anders RA, Eshleman JR, Vogelstein B, Diaz LA. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med* 2015; **372**: 2509-2520 [PMID: 26028255 DOI: 10.1056/NEJMoa1500596]

27 **Tournigand C**, André T, Bonnetain F, Chibaudel B, Lledo G, Hickish T, Tabernero J, Boni C, Bachet JB, Teixeira L, de Gramont A. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. *J Clin Oncol* 2012; **30**: 3353-3360 [PMID: 22915656 DOI: 10.1200/JCO.2012.42.5645]

28 **Shahir MA**, Lemmens VE, van de Poll-Franse LV, Voogd AC, Martijn H, Janssen-Heijnen ML. Elderly patients with rectal cancer have a higher risk of treatment-related complications and a poorer prognosis than younger patients: a population-based study. *Eur J Cancer* 2006; **42**: 3015-3021 [PMID: 16797967 DOI: 10.1016/j.ejca.2005.10.032]

29 **Akhtar R**, Chandel S, Sarotra P, Medhi B. Current status of pharmacological treatment of colorectal cancer. *World J Gastrointest Oncol* 2014; **6**: 177-183 [PMID: 24936228 DOI: 10.4251/wjgo.v6.i6.177]

30 **André T**, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, Bonetti A, Clingan P, Bridgewater J, Rivera F, de Gramont A. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 2009; **27**: 3109-3116 [PMID: 19451431 DOI: 10.1200/JCO.2008.20.6771]

31 **Golfinopoulos V**, Pentheroudakis G, Pavlidis N. Treatment of colorectal cancer in the elderly: a review of the literature. *Cancer Treat Rev* 2006; **32**: 1-8 [PMID: 16337087 DOI: 10.1016/j.ctrv.2005.10.002]

32 **Papamichael D**, Audisio R, Horiot JC, Glimelius B, Sastre J, Mitry E, Van Cutsem E, Gosney M, Köhne CH, Aapro M. Treatment of the elderly colorectal cancer patient: SIOG expert recommendations. *Ann Oncol* 2009; **20**: 5-16 [PMID: 18922882 DOI: 10.1093/annonc/mdn532]

33 **Schrag D**, Cramer LD, Bach PB, Begg CB. Age and adjuvant chemotherapy use after surgery for stage III colon cancer. *J Natl Cancer Inst* 2001; **93**: 850-857 [PMID: 11390534 DOI: 10.1093/jnci/93.11.850]

34 **Neugut AI**, Fleischauer AT, Sundararajan V, Mitra N, Heitjan DF, Jacobson JS, Grann VR. Use of adjuvant chemotherapy and radiation therapy for rectal cancer among the elderly: a population-based study. *J Clin Oncol* 2002; **20**: 2643-2650 [PMID: 12039925 DOI: 10.1200/JCO.2002.08.062]

35 **Kahn KL**, Adams JL, Weeks JC, Chrischilles EA, Schrag D, Ayanian JZ, Kiefe CI, Ganz PA, Bhoopalam N, Potosky AL, Harrington DP, Fletcher RH. Adjuvant chemotherapy use and adverse events among older patients with stage III colon cancer. *JAMA* 2010; **303**: 1037-1045 [PMID: 20233821 DOI: 10.1001/jama.2010.272]

36 **Sargent DJ**, Goldberg RM, Jacobson SD, Macdonald JS, Labianca R, Haller DG, Shepherd LE, Seitz JF, Francini G. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. *N Engl J Med* 2001; **345**: 1091-1097 [PMID: 11596588 DOI: 10.1056/NEJMoa010957]

37 **Folprecht G**, Seymour MT, Saltz L, Douillard JY, Hecker H, Stephens RJ, Maughan TS, Van Cutsem E, Rougier P, Mitry E, Schubert U, Köhne CH. Irinotecan/fluorouracil combination in first-line therapy of older and younger patients with metastatic colorectal cancer: combined analysis of 2,691 patients in randomized controlled trials. *J Clin Oncol* 2008; **26**: 1443-1451 [PMID: 18349394 DOI: 10.1200/JCO.2007.14.0509]

38 **Folprecht G**, Cunningham D, Ross P, Glimelius B, Di Costanzo F, Wils J, Scheithauer W, Rougier P, Aranda E, Hecker H, Köhne CH. Efficacy of 5-fluorouracil-based chemotherapy in elderly patients with metastatic colorectal cancer: a pooled analysis of clinical trials. *Ann Oncol* 2004; **15**: 1330-1338 [PMID: 15319237 DOI: 10.1093/annonc/mdh344]

39 **Sanoff HK**, Carpenter WR, Stürmer T, Goldberg RM, Martin CF, Fine JP, McCleary NJ, Meyerhardt JA, Niland J, Kahn KL, Schymura MJ, Schrag D. Effect of adjuvant chemotherapy on survival of patients with stage III colon cancer diagnosed after age 75 years. *J Clin Oncol* 2012; **30**: 2624-2634 [PMID: 22665536 DOI: 10.1200/JCO.2011.41.1140]

40 **Booth CM**, Nanji S, Wei X, Mackillop WJ. Management and Outcome of Colorectal Cancer Liver Metastases in Elderly Patients: A Population-Based Study. *JAMA Oncol* 2015; **1**: 1111-1119 [PMID: 26355283 DOI: 10.1001/jamaoncol.2015.2943]

**P-Reviewer:** Hoensch HP, Wojciechowska J, Lakatos PL **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** Israel

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): B, b

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

# Table 1 Patient characteristics1 *n* (%)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Study cohort  (*n =* 350) | Older (age ≥ 80 yr)  (*n =* 175) | Younger (age < 80 yr)  (*n =* 175) | *P* value |
| Median age (range) | 80 (20-99) | 83 (80-99) | 63 (20-79) | - |
| Male gender | 155 (44.3) | 84 (48) | 71 (40.6) | 0.162 |
| Ethnicity |  |  |  |  |
| Ashkenazi | 193 (56.4) | 112 (64.8) | 81 (47.9) | < 0.001 |
| Sephardic | 120 (35.1) | 58 (33.5) | 62 (36.7) |
| Arab | 12 (3.5) | 0 (0) | 12 (7.1) |
| Other | 17 (5) | 3 (1.7) | 14 (8.3) |
| 2nd malignancy | 63 (18.1) | 39 (22.4) | 24 (13.7) | 0.035 |
| Family history of cancer | 157 (51.1) | 53 (36.3) | 104 (64.6) | < 0.001 |
| Family history of CRC | 65 (21.2) | 21 (14.4) | 44 (27.3) | 0.006 |
| IBD | 1 (0.3) | 1 (0.6) | 0 (0) | 0.335 |
| Polyps2 | 122 (35.4) | 55 (33.2) | 67 (38.5) | 0.233 |
| HNPCC/FAP | 9 (2.7) | 5 (3) | 4 (2.4) | 0.695 |
| Smoking history | 104 (34.9) | 41 (24.6) | 74 (44.3) | < 0.001 |
| Diagnosis d/t screening | 45 (12.9) | 10 (5.7) | 35 (20) | < 0.001 |
| Performance status3 of 0-1 | 268 (82.5) | 115 (71) | 153 (93.9) | < 0.001 |

1Valid percentages. Missing data as follows: ethnicity (*n =* 8); 2nd malignancy (*n =* 1); family history of malignancy (*n =* 43); family history of CRC (*n =* 43); IBD (*n =* 5), polyps (*n =* 5); HNPCC/FAP (*n =* 14); smoking history (*n =* 16), performance status (*n =* 25); 2Polyps- diagnosis of polyps before or during CRC diagnosis; 3Performance status was determined according to the Eastern Cooperative Oncology Group score during the first encounter with the oncologist. CRC: Colorectal cancer; IBD: Inflammatory bowel disease; FAP*:* Familial adenomatous polyposis; HNPCC: Hereditary non-polyposis colorectal cancer; d/t: due to.

**Table 2 Tumor characteristics1 *n* (%)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Study cohort  (*n =* 350) | Older (age ≥ 80 yr)  (*n =* 175) | Younger (age < 80 yr)  (*n =* 175) | *P* value |
| Tumor location2  Right colon  Left colon/Rectum | 140 (40)  210 (60) | 80 (45.7)  95 (54.3) | 60 (34.3)  115 (65.7) | 0.029 |
| Histology  NOS  Mucinous  Signet ring cell  Other | 260 (76.5)  64 (18.8)  11 (3.2)  5 (1.5) | 124 (74.2)  38 (22.8)  3 (1.8)  2 (1.2) | 136 (78.6)  26 (15)  8 (4.6)  3 (1.78) | 0.201 |
| Grade3  1  2-3 | 48 (14.8)  276 (85.2) | 17 (10.4)  146 (89.3) | 31 (19.3)  130 (80.7) | 0.025 |
| T  T1  T2  T3  T4 | 17 (5.2)  57 (17.6)  237 (73.2)  13 (4) | 5 (3.1)  28 (17.4)  123 (76.4)  5 (3.1) | 12 (7.4)  29 (17.8)  114 (69.9)  8 (4.9) | 0.27 |
| N  N0  N1  N2 | 179 (67)  56 (21)  32 (12) | 94 (71.2)  24 (18.2)  14 (10.6) | 85 (63)  32 (23.7)  18 (13.3) | 0.357 |
| M1 | 72 (20.7) | 34 (19.8) | 38 (21.7) | 0.655 |
| TNM stage  I  II  III  IV | 65 (19)  116 (33.8)  90 (26.2)  72 (21) | 30 (17.7)  66 (38.8)  40 (23.5)  34 (20) | 35 (20.2)  50 (28.9)  50 (28.9 )  38 (22) | 0.259 |
| LVI | 18 (6) | 11 (7.5) | 7 (4.6) | 0.296 |
| VVI | 36 (11.9) | 15 (10.1) | 21 (13.6) | 0.348 |
| Obstruction4 | 36 (10.3) | 22 (12.6) | 14 (8) | 0.159 |
| Perforation4 | 12 (3.4) | 10 (5.7) | 2 (1.1) | 0.019 |
| Synchronous CRC | 11 (3.1) | 4 (2.3) | 7 (4) | 0.358 |
| Metachronous CRC | 2 (0.6) | 1 (0.6) | 1 (0.6) | 0.997 |
| RAS mutated | 8 (22.2) | 2 (15.4) | 6 (26.1) | 0.458 |
| BRAF mutated | 1 (3.7) | 0 (0) | 1 (7.7) | 0.29 |
| MSI-H | 6 (25) | 3 (100) | 3 (14.3) | 0.001 |

1Valid percentages. Missing data as follows: histology (*n =* 10); grade (*n =* 26); T stage (*n =* 26); N status (*n =* 83); M status (*n =* 3); TNM stage (*n =* 7); lymphatic invasion (*n =* 51); vascular invasion (*n =* 48); metachronous tumor (*n =* 1); KRAS (*n =* 314); BRAF (*n =* 323); MSI-H (*n =* 326); 2Right colo*n =* appendix, ascending colon and transverse colon, Left colo*n =* descending colon and sigma; 3Grade 1= well differentiated, grade 2 moderately differentiated, poorly differentiated; 4Obstruction or perforation at presentation. CRC: Colorectal cancer; NOS: Not otherwise specified; LVI: Lymphovascular invasion; VVI: Venovascular invasion; MSI-H: Microsatellite instability- high.

**Table 3 Treatment1**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Study cohort | Older (age ≥ 80 yr) | Younger (age < 80 yr) | *P* value |
| No. of LN dissected, mean (SD)2 | 14.4 (6.1) | 14.3 (5.4) | 14.4 (6.8) | 0.893 |
| Adjuvant/neoadjuvant Tx2 | 119/271 (43.9) | 38/138 (27.5) | 81/133 (60.9) | <0.0001 |
| Oxaliplatin-basedadjuvant chemotherapy2 | 58/116 (50) | 11/37 (29.7) | 47 (59.5) | 0.002 |
| No. of chemotherapy lines in stage IV3  0  1  ≥2 | 12 (20)  24 (40)  24 (40) | 9 (34.6)  11 (42.3)  6 (23.1) | 3 (8.8)  13 (38.2)  18 (53) | 0.016 |
| Type of chemotherapy in stage IV, 1st line3,4  Fluoropyrimidine  Fluoropyrimidine+oxaliplatin/irinotecan | 11 (21.6)  40 (78.4) | 6 (30)  14 (70) | 5 (16.1)  26 (80.9) | 0.239 |
| Local interventions to metastatic sites5  None  Surgery ± other local intervention  Other local intervention | 45 (57)  31 (39.2)  3 (3.8) | 28 (90.3)  2 (6.5)  1 (3.2) | 17 (35.4)  29 (60.4)  2 (4.2) | < 0.001 |
| Hematological toxicity, grade ≥ 3 | 17 (11) | 4 (8) | 13 (12.5) | 0.404 |
| Non-hematological toxicity, grade ≥ 3 | 37 (23.6) | 9 (18) | 28 (26.7) | 0.261 |

1Valid percentages. Missing data as follows: adjuvant/neoadjuvant treatment (*n =* 4); no. of lymph nodes dissected (*n =* 20); type of chemotherapy (*n =* 7); no. of chemotherapy lines (*n =* 12); local intervention to a metastatic site (*n =* 4), hematological toxicity (*n =* 19); non-hematological toxicity (*n =* 19); 2Data regarding patients who presented with non-metastatic disease; 3Data regarding patients who presented with metastatic disease; 4Chemotherapy was given with or without a biological agent including bevacizumab, cetuximab or panitumumab; 5Local intervention to a metastatic site included: radiofrequency ablation, chemoembolization, intra-arterial chemotherapy, stereotactic body irradiation, and radiotherapy. LN: lymph nodes; Tx: treatment.

**Table 4 Univariate and Multivariate analyses of cancer specific survival and disease free survival**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Univariate analysis CSS1 | | Multivariateanalysis CSS1,2 | | Univariate analysis DFS3 | | Multivariate analysis DFS2,3 | |
|  | **5-yr CSS** | ***P* value** | **Hazard ratio** | ***P* value** | **5-yr DFS** | ***P* value** | **Hazard ratio** | ***P* value** |
| Age, yr  ≥ 80  < 80 | 63%  78% | 0.009 | 1.7 (0.8-3.6) | 0.155 | 71%  79% | 0.226 | 1.2 (0.5-2.9) | 0.668 |
| Gender  Male  Female | 68%  73% | 0.274 | 0.9 (0.5-1.6) | 0.762 | 77%  74% | 0.682 | 1.1 (0.5-2.2) | 0.865 |
| Ethnicity  Ashkenazi  Sephardic  Arab  Other | 73%  65%  88%  79% | 0.293 | - | - | 73%  78%  69%  93% | 0.608 | - | - |
| Second malignancies  Yes  No | 75%  70% | 0.497 | - | - | 81%  74% | 0.429 | - | - |
| Family hx of cancer  Yes  No | 78%  68% | 0.068 | - | - | 82%  71% | 0.096 | - | - |
| Family hx of CRC  Yes  No | 86%  70% | 0.024 | 0.3 (0.1-0.8) | 0.015 | 91%  73% | 0.048 | 0. 2 (0.1-0.8) | 0.016 |
| Performance status  0-1  2-4 | 77%  53% | 0.0003 | 1.2 (0.5-3) | 0.62 | 78%  60% | 0.068 | 2.1 (0.7-6.3) | 0.175 |
| Mode of Diagnosis  Symptoms  Screening | 68%  90% | 0.024 | 1 (0.3-3.4) | 0.973 | 74%  85% | 0.235 | - | - |
| Tumor location  Right colon  Left colon/Rectum | 66%  75% | 0.102 | - | - | 77%  75% | 0.723 | - | - |
| Histology NOS/mucinous/other  Signet ring cell | 74%  33% | < 0.0001 | 5.7 (1.5-21.1) | 0.009 | 77%  48% | < 0.0001 | 6.9 (1.7-28) | 0.007 |
| Grade  1  2-3 | 87%  69% | 0.05 | - | - | 71%  76% | 0.561 | - | - |
| T  T1  T2  T3  T4 | 92%  90%  73%  39% | < 0.0001 | - | - | 100%  82%  72%  76% | < 0.0001 | - | - |
| N  N0  N1  N2 | 89%  79%  56% | 0.0003 | - | - | 81%  72%  57% | 0.001 | - | - |
| M  M0  M1 | 85%  26% | < 0.0001 | - | - | - | - | - | - |
| TNM stage  I  II  III  IV | 94%  90%  73%  26% | < 0.0001 | 1  1.9 (0.4-8.7)  6.7 (1.5-30.1)  20 (4.6-87.6) | -  0.433  0.013  <0.0001 | 90%  77%  63%  - | 0.014 | 1  3.5 (0.8-15.6)  8.4 (1.9-36.4)  - | -  0.107  0.004  - |
| LVI  Yes  No | 57%  75% | 0.073 | - | - | 79%  75% | 0.848 | - | - |
| VVI  Yes  No | 65%  75% | 0.272 | - | - | 72%  76% | 0.791 | - | - |
| Obstruction  Yes  No | 49%  74% | 0.001 | 2.3 (0.99-5.4) | 0.052 | 49%  79% | 0.001 | 2.95  (1.1-7.9) | 0.03 |
| Perforation  Yes  No | 28%  73% | 0.0001 | 3.5 (1.1-10.9) | 0.028 | 64%  76% | 0.262 | - | - |
| Adjuvant/neoadjuvant tx  Yes  No | 87%  78% | 0.137 | - | - | 72%  80% | 0.236 | - | - |
| Local Tx to metastatic sites  Yes  No | 41%  20% | 0.007 | - | - | - | - | - | - |

1Univariate and multivariate analysis for CSS were performed for patients with stage I-IV; 2Multivariate analysis was calculated for the entire follow-up period. The column of multivariate analysis depicts only factors that were included in the model; 3Univariate and multivariate analysis for DFS were performed for patients with stage I-III. DFS: Disease free survival; CRC: Colorectal cancer; CSS: Cancer specific survival; LVI: Lymphovascular invasion; NA: Not applicable; NOS: Not otherwise specified; Tx: Treatment; VVI: Venovascular invasion.



*P* < 0.0001

**OS**

**t/mo**

Age group:

----- < 80

----- ≥ 80

ddddd

**Figure 1 Overall survival.** OS: Overall survival.



*P* = 0.009

**t/mo**

Age group:

----- < 80

----- ≥ 80

ddddd

**CSS**

**Figure 2 Cancer specific survival.** CSS: Cancer specific survival.