A retrospective analysis of toxicity and outcomes following chemotherapy for the older population at a single institution

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Abstract:

Introduction: Surgical treatment of colorectal cancer (CRC) in elderly patients has improved, but data on adjuvant and palliative chemotherapy tolerability and benefits in this growing population remains scarce. The elderly population is mostly underrepresented in clinical trials and results for this group of patients are seldom reported separately.

Patients and method: Using a retrospective study, we analyzed demographics, compared toxicities in the age groups < 70 years and ≥ 70 years in colorectal cancer patients at Tygerberg Hospital (South Africa). We assessed tumor related mortality, progression free survival (PFS) and overall survival (OS) including predictive factors of OS.

Results: A total of 50 patients received either adjuvant or palliative chemotherapy. Different chemotherapy regimens were used. There was no difference in overall or severe (Common Toxicity Criteria Grades 3-4) toxicity in both age groups. Out of the 50 patients, 8 (16%) had Grade 3-4 toxicity. Of these 4 (15%) were < 70years, 4 (17%) were ≥ 70 years. The progression free survival (PFS) and overall survival (OS) were measured using Kaplan-Meier curves. The mean follow-up time was 47.5 months (range: 14.4-80.8 months, 95% CI 41.5-53.5 months). The 5-year overall survival rate for Stage II&III patients <70 years and ≥70 years were 80.9% and 69.5%, respectively, and not significantly different; P=0.5156; HR=0.65 (95% CI: 0.17-2.41). Also, no statistically significant difference emerged between the 5-year progression free survival rates of 70.7% and 58.8%; P=0.4920; HR=0.68 (95% CI: 0.23-2.04). For Stage IV patients, there were no significant differences in survival in both groups. There were no survivors beyond 40 months. Median survival rates were similar at 16.3 months (for < 70 years) and 15.9 months (for ≥ 70 years); P=0.8105; HR=1.14(95% CI: 0.35-3.81). There were also no progression free survivors beyond 23 months. Median PF survival rates were 11.1 months (for < 70 years) and 13.5 months (for ≥ 70 years), and were not significantly different; P=0.1743; HR=1.99 (95% CI: 0.66-9.67).

Weight loss and performance status (PS) were evaluated as potential predictive factors of OS. For Stage II&III patients of <70 and ≥70 years of age, 68 and 84% of patients presented with a weight loss of <5%, respectively. The corresponding proportions of Stage IV patients were 75 and 100%. Also, 84 and 100% of Stage II&III patients <70 and ≥70 years, respectively, had a PS of 1. All Stage IV patients had a PS of 1.

Conclusion: "Fit" elderly patients benefit, at least to the same extent, from adjuvant and palliative chemotherapy as younger patients in this cohort. Therefore, standardized adjuvant and palliative chemotherapy could be offered to elderly patients and they should not be excluded from clinical trials.

Keywords: Elderly population; chemotherapy; toxicity; progression free survival; overall survival

Introduction

Colorectal cancer (CRC) accounts for 10% of cancer diagnoses and deaths. It is the third most common cause of cancer deaths in the world. [(1)] It is estimated that 136 830 new patients are diagnosed with large bowel cancer each year in the United States. This constitutes about 96 830 cases of colon cancer and 40 000 cases of rectal cancers. The expected deaths due to large bowel cancers are estimated to be 50 310 Americans annually.[(2)(3)] Colorectal cancer (CRC) usually affects older people with 67 to 75% being ≥ 65 years.[(4)(5)] The average age at diagnosis is 72 years, with 70% of patients > 65 years and 40% older than 75 years.[(6)(7)(8)]

The fastest growing proportion of the population in western countries is those older than 65 years. This translates to more people living longer who have the potential to develop a malignancy. The result is an increase in elderly CRC patients that require treatment. [(9)]

The mainstay of treatment for stage I and stage II colon cancer is surgery, although a specific subset of stage II colon cancer will require adjuvant chemotherapy. [(10)] The standard of care for stage III colon cancer is surgery, followed by adjuvant chemotherapy. [(11)(12)] Stage IV colorectal cancer is best treated with systemic chemotherapy to prolong survival and also to help improve symptoms and quality of life. A systematic review undertaken by the Colorectal Cancer

Collaborative Group compared palliative chemotherapy with supportive care and it revealed an improvement of 3.7 months in median survival in favor of the chemotherapy arm.[13]

Older patients are usually not included in clinical trial recruitment. In a review of 495 National Cancer Institute-Sponsored Cooperative Group trials from 1997 – 2000, the older patients with CRC were clearly under-represented in phase II and III clinical trials. [14] The reason why older patients are under-staged and undertreated is multifactorial. An increase in age is usually associated with co-morbidities, reduction in organ function, and a decline in cognitive or socio-economic abilities. [15]

The definition of "elderly/older" patients can range between $\geq$ 65 years to $\geq$ 80 years in different trials. Many authors, however, agree that a cut-off age of 70 is sufficient in a clinical trial set-up. [16]

For over 40 years, 5-Fluorouracil (5-FU) was the only effective drug with no second line options. In the past ten years numerous new cytotoxic and biologic drugs became available. This resulted in the survival rate increasing from 10-12 months. [17]

There are numerous data to support the benefit for metastatic colorectal cancer patients, in terms of overall survival, when the three most active cytotoxic drugs (5- Fluorouracil/ Leucovorin, oxaliplatin and irinotecan) are given sequentially or concomitantly. [18][19][20] A meta–analysis performed by Folprecht confirmed that patients $\geq$70 years with metastatic colorectal cancer respond as well as younger patients to 5-Fluorouracil based regimes. The overall survival in both groups was similar (10.8 months versus 11.3 months, respectively). [15]

At our institution, the standard of care for high risk stage II and stage III colon cancer patients is surgery followed by adjuvant 5-FU-based chemotherapy for six to eight cycles. Either complete local excision or total mesorectal excision (TME) is the choice of treatment for patients with early localised rectal cancer (stage 1). Stage II and stage III (locally advanced) rectal cancers receive neoadjuvant chemoradiation followed by surgery six to eight weeks later. The presence of lymph nodes determines the need for adjuvant 5-FU-based chemotherapy. Stage IV CRC patients get 5-FU-based chemotherapy upfront. The two most commonly used regimes are either

bolus 5-FU (425 mg/m^2)/Leucovorin (LV) (20 mg/m^2) given intravenously per day for 5 days (four weekly) or continuous infusion of 5-FU (1 g/m^2) for 4 days (four weekly).

The chosen regime usually depends on the availability of beds, rather than physician or patient choice. The availability of oxaliplatin, irinotecan, capecitabine and biological agents are restricted to specific subgroups of patients due to cost constraints in this resource limited setting.

The use of 5-FU chemotherapy is associated with numerous toxicities, including: myelosuppression, mucositis, diarrhea, hand and foot syndrome, cardiac symptoms, and tear duct stenosis, acute and chronic conjunctivitis. [21]

5-FU chemotherapy is contraindicated in patients with the following co-morbidities: ischemic heart disease, cerebro-vascular accident within the previous 6 months, renal failure, active pulmonary tuberculosis, and poor insight.

There are no published data available on the tolerability and benefits of adjuvant and palliative chemotherapy for CRC in the older population at Tygerberg Hospital. Taking into account the poor socio-economic status of the majority of the target population, resulting in advanced stage at diagnoses, poor nutritional reserves and associated co-morbidities like human immunodeficiency virus (HIV) and pulmonary tuberculosis, there is a need to compare South African data with published literature.

Rationale of the Study

The majority of patients referred to the Department Clinical and Radiation Oncology, Tygerberg Hospital (South Africa), with histologically confirmed adenocarcinoma of the colon/rectum presented with a locally advanced or metastatic stage. Due to the advanced stage at presentation, most of the newly diagnosed CRC patients needed systemic chemotherapy. The standard practice at our institution is 5-FU-based chemotherapy.

There was a wide range regarding the age at presentation ranging from < 40 years to the more predicted ≥70 years. Most of the patients came from a low socio-economic background with a poor nutritional status and a decreased functional capacity at baseline.

There is limited data on the safety and efficacy of chemotherapy in the older "real world" population, [6] although there are numerous trials that indicated that older patients do experience the same benefit as the younger population with similar toxicities. [22] Unfortunately, most of the clinical trials do not include elderly patients, and the few included in trials were carefully selected and not representing the average elderly patient. This again results in a knowledge gap for the treating oncologist.

Aim

To retrospectively evaluate the differences in toxicities and tumor-related mortality in two different age groups of patients (< 70 and ≥ 70 years), with histologically proven adenocarcinoma of colon/rectum, referred to the department between January 2009 and December 2013.

Objectives

To evaluate patient and tumor characteristics. To assess toxicities experienced from chemotherapy, tumor-related mortality, PFS, OS, and predictive factors (weight loss and performance status) for OS in the 2 different age groups.

Methodology

Patient records

We performed a retrospective, observational study in the Department of Clinical and Radiation Oncology at Tygerberg Hospital (South Africa). All patients referred with histologically proven adenocarcinoma of the rectum/colon who received chemotherapy between January 2009 and December 2013 were included in the study. Two hundred and sixty files were reviewed. Two hundred and ten files for patients who did not receive chemotherapy or those who received chemotherapy but had incomplete records (data/files missing) were excluded. The remaining 50 files were evaluated in this study.

The relevant data were collected from the therapy folders. Data from imaging studies were collected from the Picture Archiving and Communications System (PACS) system, and the laboratory results were collected from the DISALAB program.

Data were collected using the patient's folder number only and no name or identifiable information was used. The collected data included the age, gender, tumor characteristics (localization, grade, extension, stage), treatment, co-morbidities, HIV status, performance status (PS), weight loss, alkaline phosphatase, the number of metastatic sites, time since diagnosis to start of treatment, toxicities due to chemotherapy, and if the chemotherapy course was completed or not. The causes why the chemotherapy was stopped, if applicable, and also the cause of death were also recorded. The toxicities associated with chemotherapy were recorded according to Common Toxicity Criteria.

Statistical analysis

A statistician was involved and all the data were collected in coded questionnaires and analyzed, using the GraphPad Prism software (San Diego, USA). Progression free and overall survival rates, as well as, predictive factors for overall survival were presented and compared, using Kaplan-Meier curves. Analytical statistics were calculated to assess associations between variables and the findings were presented in tables and graphs. Descriptive statistics were used to present the different variables within the data set. These were presented in the form of tables, as well as graphically.

Ethical considerations

Approval was granted for the study by Human Research Ethics Committee of University of Stellenbosch (Ethics Ref: S15/02/040). Patient records were reviewed with utmost confidentiality. The individual's data set was allocated a unique study number and the data were stored in a secure office, as well as, on a computer to which only the principal investigator had access via a password.

Results

Patients and tumor characteristics

Of the 50 patients, 29 (58%) were male and 21 (42%) were female. Age at diagnosis ranged from 28 to 78 years (mean of 62 years). Twenty-seven (54%) of the patients were aged < 70 years, and 23 (46%) were aged ≥70 years. Most of the patients, 47 (94%), had World Health Organisation

performance status (PS) of 1. Three (6%) patients had ECOG PS of 2. Patient characteristics are shown in Table 1.

Table 1 : Patient Characteristics

Characteristic	No of Patients (%)
Age	
<70 yrs.	27(54%)
≥70 yrs.	23(46%)
ECOG PS	
1	**47(94%)**
2	**3(6%)**
Sex	
Male	29(58%)
Female	21(42%)

Data for tumor characteristics and treatment options are summarized in Table 2. Of the 50 patients, 22 had colon cancers and subsites included the left, right and sigmoid colon. The remainder of the patients had rectal cancer. Most patients (36 out of 50) had Grade 2 adenocarcinoma. Eight patients had grade 1, and 2 patients had grade 3 tumors. Four patients had tumors of unknown grade.

Out of the 50 patients, 28 patients had stage III disease at diagnosis. Ten patients had stage II disease and 12 patients had stage IV disease.

All 50 patients received different regimens of chemotherapy which included 5-FU/LV bolus, 5-FU infusion and Capecitabine. Two patients did not finish the 6 cycles of chemotherapy due to neutopneanic sepsis. Forty-six patients had surgery and 34 had radiotherapy.

Out of 50 patients, 21 patients had hypertension, 3 had pulmonary tuberculosis, 2 had ischaemic heart disease, 3 had deep vein thrombosis, 3 had diabetes mellitus type 2, and 18 had no comorbidities.

Table 2. Tumor Characteristics and therapeutic approach

Characteristic	<70 yrs. (n=27)	≥ 70 yrs.(n=23)
Gender		
Male	14(52%)	15(65%)
Female	13(48%)	8(35%)
Localization		
Colon	13(48%)	9(39%)
Rectum	14(52%)	14(61%)
Differentiation		
I	5(19%)	3(13%)
II	18(67%)	18(78%)
III	1 (4%)	1(4%)
Unknown	3(11%)	1(4%)
Tumor stage at diagnosis		
II	6(22%)	4(17%)
III	15(56%)	13(57%)
IV	6(22%)	6(26%)
Treatment		
Surgery	24(89%)	22(96%)
Radiotherapy	17(63%)	17(74%)
Chemotherapy	27(100%)	23(100%)
Weight loss < 5%	22(81%)	17(74%)
Weight loss > 5%	5(19%)	6(26%)
Comorbidities		
None	15(56%)	3(13%)
Hypertension	7(25%)	14(61%)
PTB	1(4%)	2(9%)
Heart disease	1(4%)	1(4%)
Diabetes mellitus	0	3(13%)
Deep vein thrombosis	3(11%)	0

Tumor related mortality

Tumor related mortality was assessed using univariate and multivariate analysis. Univariate analysis demonstrated that patients with rectal cancer, with stage III, stage IV and those who had surgery had a higher mortality related risk, as shown in Table 3. Gender, age, comorbidity, and radiotherapy did not play a significant role in tumor related mortality.

Table 3: Univariate analysis on risk factors for tumor related mortality.

Characteristic	Hazard ratio*	P-value	95% CI
Male	1.0		
Female	1.08	0.86	0.45-2.57
Colon	1.0		
Rectum	0.38	0.03	0.16-0.92
Stage II	1.0		
Stage III	6.14	0.007	1.62-23.20
Stage IV	13.32	<0.0001	3.62-49.17
<70 years	1.0		
≥70 years	0.75	0.67	0.13-2.79
No comorbidity	1.0		
Comorbidities	1.48	0.92	0.57-3.81
No surgery	1.0		
Surgery	0.1	<0.0001	0.03-0.32
No radiotherapy	1.0		
Radiotherapy	0.94	0.88	0.38-2.32

*Hazard ratio of 1.0 implies reference value. For example, patients with regional and disseminated disease were respectively ~6 and ~13 times more likely die from the disease than those with localized tumors.

From multivariate analysis, only patients with stage III and stage IV disease were at a higher mortality related risk, as presented in Table 4. There was no difference in tumor related mortality risk in relation to age, gender, surgery, radiotherapy, and subsite of disease.

Table 4: Multivariate analysis on risk factors for tumor related mortality.

Characteristic	Hazard ratio*	P-value	95% CI
Male	1.0		
Female	0.9	0.85	0.75-2.85
Colon	1.0		
Rectum	0.49	0.35	0.11-2.83
Stage II	1.0		
Stage III	5.61	0.017	1.35-23.26
Stage IV	9.22	0.009	1.73-49.11
<70 years	1.0		
≥70years	0.81	0.79	0.13-7.02
No comorbidity	1.0		
Comorbidities	1.01	0.98	0.29-3.49
No surgery	1.0		
Surgery	0.26	0.10	0.05-1.32
No radiotherapy	1.0		
Radiotherapy	2.75	0.95	0.68-11.06

*Hazard ratio of 1.0 implies reference value. For example, patients with stage III and stage IV disease were respectively ~6 and ~9 times more likely die from the disease than those with stage II tumors.

Toxicities from chemotherapy in different age groups

Out of the 50 patients, 8 (16%) had Grade 3-4 toxicity. Divided by age, 4 patients (15%) were <70 years and 4 (17%) were ≥70 years. Of the 50 patients, 36 (72%) had Grade 1-2 toxicity, 17 (63%) were < 70 years and 19(83%) were ≥ 70 years.

Neutropaenic sepsis was experienced in 6 patients (3 patients < 70 years (11%); 3 patients (13%) ≥70 years). Table 5 shows the distribution and types of toxicities experienced for this population by age group. Both age groups experienced similar toxicity. Table 6 displays maximum toxicity grade and age.

Table 5 .Distribution and Types of Toxicity by Age

Toxicity type	<70 yrs. (n=27)	≥ 70 yrs.(n=23)
Nausea and vomiting		
Grade 0	17(63%)	14(52%)
Grade 1-2	9(33%)	8(30%)
Grade 3-4	1(4%)	1(4%)
Diarrhea		
Grade 0	18(67%)	13(57%)
Grade 1-2	8(30%)	9(39%)
Grade 3-4	1(4%)	1(4%)
Dermatitis		
Grade 0	27(100%)	21(91%)
Grade 1-2	0	2(8%)
Grade 3-4	0	0
Hand + foot syndrome		
Grade 0	25(93%)	21(91%)
Grade 1-2	0	0
Grade 3-4	2(7%)	2(8%)
Neutropaenic sepsis		
None	24(89%)	20(87%)
Present	3 (11%)	3(13%)

Table 6 :Maximum toxicity grade by age group

Maximum toxicity grade	<70 yrs.	≥ 70 yrs.
0	1	1
1	12	10
2	10	9
3	2	1
4	2	2
Total	27	23

Survival

The progression free survival (PFS) and overall survival (OS) were measured using Kaplan-Meier curves**.** The mean follow-up time was 47.5 months (range: 14.4-80.8 months, 95% CI 41.5-53.5 months). Figure 1A shows OS for Stage IV patients, showing no significant differences in survival in both groups. No survivors beyond 40 months. Median survival: 16.3 months (for < 70 years) and 15.9 months (for ≥ 70 years); P=0.8105; HR=1.14(95% CI: 0.35-3.81). Figure 1B shows PFS for Stage IV patients, showing no significant differences in survival in both groups. There were no progression free survivors beyond 23 months. Median PF survival: 11.1 months (for < 70 years) and 13.5 months (for ≥ 70 years); P=0.1743; HR=1.99(95% CI: 0.66-9.67).

Figure 2A shows OS for stage II &III patients, showing no significant differences in survival in both groups. The 5-year overall survival rate for patients <70 years and ≥70 years were 80.9% and 69.5%, respectively; P=0.5156; HR=0.65(95% CI: 0.17-2.41). Figure 2B shows PFS for stage II&III patients, showing no significant differences in survival in both groups. The 5-year progression free survival rate for patients <70 years and ≥70 years were 70.7% and 58.8%; P=0.4920; HR=0.68(95% CI: 0.23-2.04).

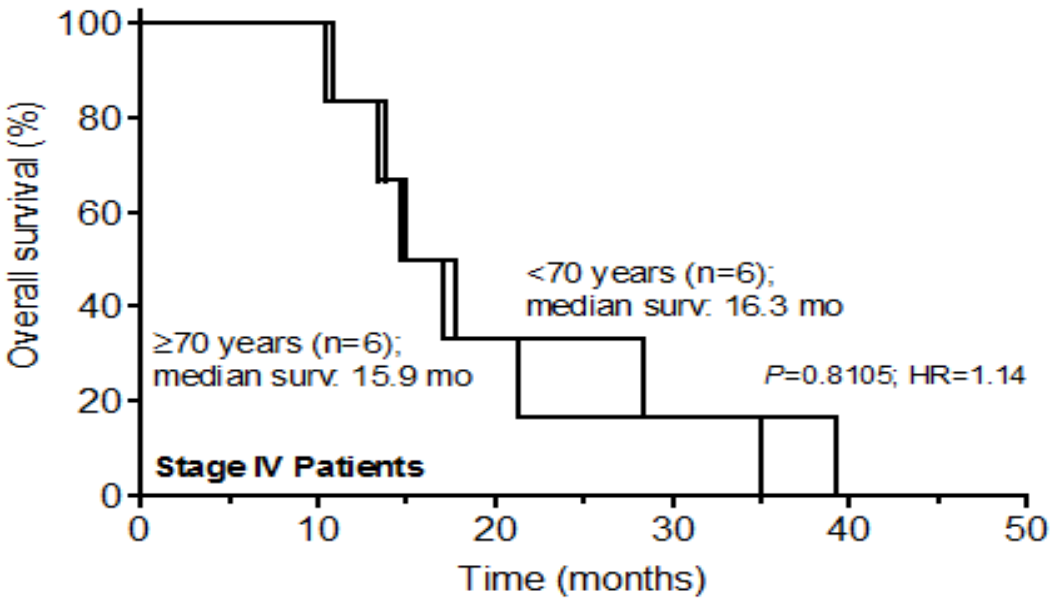

Figure1A. Overall survival rates for Stage IV colorectal cancer patients in age groups <70 years and ≥70 years.

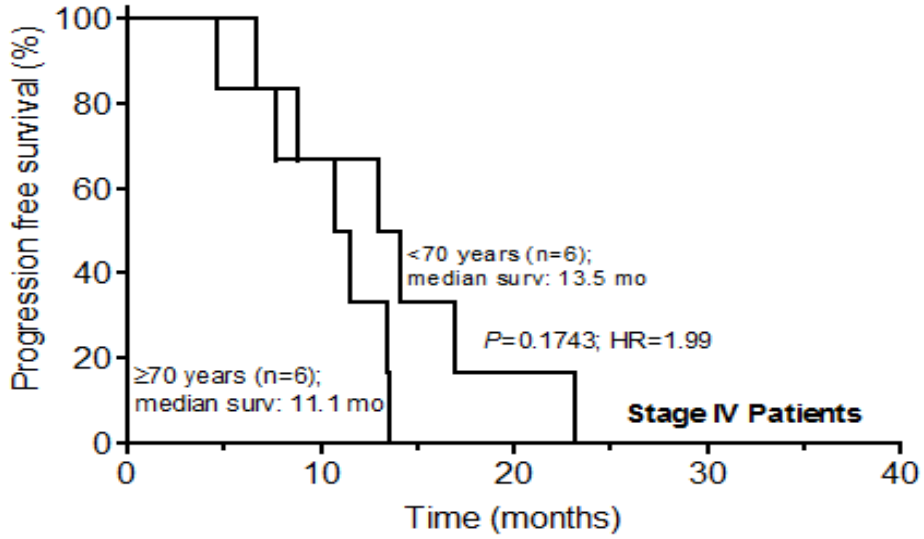

Figure 1B. Progression free survival rate for Stage IV colorectal cancer patients in age groups <70 years and ≥70 years.

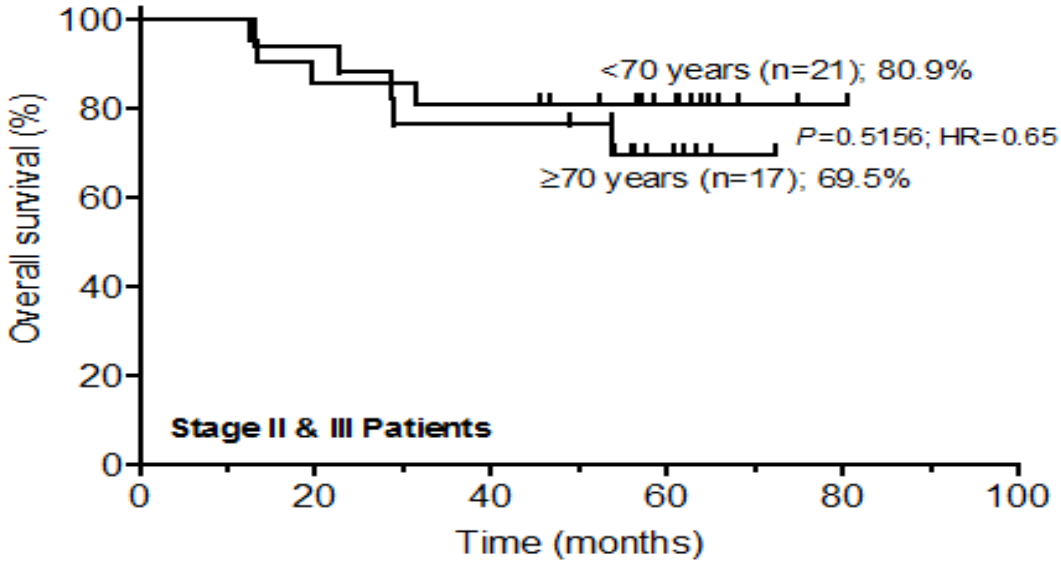

Figure 2A. Overall survival rate at 5 years for Stage II &III colorectal cancer patients in age groups <70 years and ≥70 years.

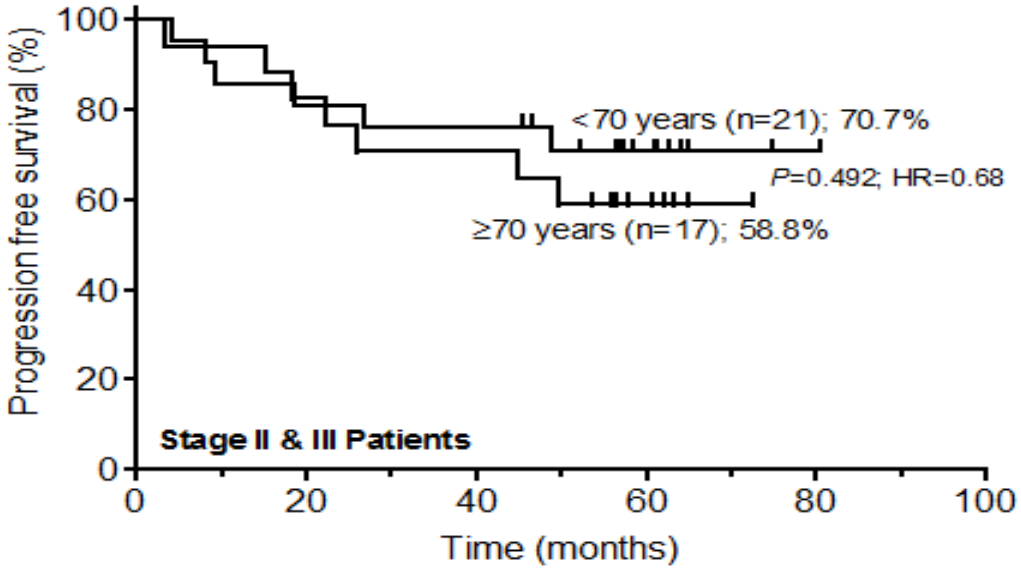

Figure 2B. Progression free survival rate at 5 years for Stage II &III colorectal cancer patients in age groups <70 years and ≥70 years.

The distributions of predictive factors of OS are presented in Table 7. Sixty-eight and 84% of Stage II&III patients in the <70 and ≥70 years age groups presented with less than 5% weight loss, respectively. For Stage IV patients, the corresponding proportions for the two age groups were 75% and 100%. Similarly, 84% and 100% of Stage II&III patients in the <70 and ≥70 years groups, respectively, had a PS of 1. All Stage IV patients had a PS of 1.

Table 7: Distribution of factors associated with better overall survival.

Age group	Tumour stage	Weight loss (%)		Performance status	
		< 5	> 5	1	2
< 70 years	II & III	13	6	16	3
	IV	6	2	8	0
≥ 70 years	II&III	16	3	19	0
	IV	4	0	4	0

Discussion

This study reports on toxicities and outcomes of histologically proven colorectal cancer in elderly patients at Tygerberg Hospital who received chemotherapy between January 2009 to December 2013. Most of the patients had either locally advanced disease or metastatic disease, and needed chemotherapy treatment. The reason for late presentation maybe due to late diagnosis in a resource limited environment or a poor referral system.

In the current study, our study population was divided into two groups <70 years and ≥70 years. This is consistent with previous studies which also divided their studies into two age groups. [15][27] The limitation of our study is the small numbers of patients. As such, toxicity data is presented in a descriptive manner and do not seem to show marked differences between the two age groups.

Kohne *et al* reported the average age of patients diagnosed with CRC in the United States in 2008 to be 71 years. The incidence of CRC was 40% among patients older than 75 years. [6] This is similar to the current study, as 32% of our study population was >75 years. More elderly patients are included into studies compared to the past due to an increase in the number of patients undergoing curative resections for CRC, as well as, an associated decrease in post-operative mortality.[6] A few studies have shown underrepresentation of elderly patients above 75 years old.[15][27]

Serra-Rexach *et al* assessed tumor-related mortality using Kaplan-Meier survival curve analysis. After a median follow-up of 36.5 months, younger patients had a longer tumor-specific survival time than older patients (36.41 months versus 26.05 months). Younger patients had a lower tumor-specific mortality risk than older patients. [27] In our study, there was no difference in tumor-related mortality risk between both groups. In addition, the above study reported patients with stage III and stage IV diseases and who did not undergo surgery to have a higher tumor related mortality risk. [27] In our study, multivariate analysis shows that patients with stage III and stage IV diseases were at a higher risk of tumor-related mortality. Surgery did not statistically influence the tumor-related mortality risk.

The results of the current analysis are consistent with those of previous studies showing the efficacy and effectiveness of chemotherapy. Sargent *et al* compiled a pooled analysis of adjuvant chemotherapy for colon cancer in the older population to measure the incidence of side effects like nausea or vomiting, diarrhea, stomatitis, and leukopenia. Elderly patients (>70 years) did not experience more side effects, except for a decrease in leukocytes.[28] In this study, we analyzed the incidence of side effects like nausea and vomiting, hand and foot syndrome, dermatitis, diarrhea and neutropaenic sepsis. Both age groups experienced similar toxicity. This is consistent with the published literature. [28] We, however, did not compare the severity of these side effects between different types of chemotherapy regimens as other studies have done in the past. In our environment, we mainly use 5-FU continuous infusion or 5-FU/LV bolus therapy. This is due to the limited resources available.

The results of this cohort demonstrate the 5-year overall survival rate for patients <70 years and ≥70 years were 80.9% and 69.5%, respectively; P=0.5156; HR=0.65(95% CI: 0.17-2.41) for stage II&III patients, showing no significant differences in survival in both groups. The 5-year

progression free survival rate for patients <70 years and ≥70 years were 70.7% and 58.8%; P=0.4920; HR=0.68(95% CI: 0.23-2.04). Showing no significant differences in survival in both groups.

Our data suggest that chemotherapy in elderly patients with CRC is well tolerated as nearly half of the study population was older than 70 years. This is consistent with the published literature.[15][27] Careful selection of patients is probably more important in the elderly group, and in this study 94% had an ECOG PS of 1. In the palliative setting, patients with good PS are the ones likely to profit from chemotherapy, and treatment should start as soon as possible before their PS deteriorates.

The absence of significant differences in overall survival between the two age groups, regardless of disease stage, may be attributed to the finding that the degree of weight loss and performance status (PS) for both groups was comparable and that the study cohort was reasonably healthy. Put together, our study shows that two factors, namely, weight loss and performance status appear to be independently associated with a better OS.

Strengths and Weaknesses

The main strength of this study is the demonstration of a tolerability of chemotherapy in the elderly CRC patients, contrary to popular belief. Weaknesses of the study included the retrospective nature of the study and being a single center study. Exclusion of a large number of patients due to incomplete records was a major limitation of this study. Another weakness of the study is that the compared groups were not matched in size, reducing the reliability of the statistical conclusions arrived at.

Conclusion

“Fit” elderly colorectal cancer patients benefit, at least to the same extent, from adjuvant and palliative chemotherapy as younger patients in our cohort. Therefore, standardized adjuvant and palliative chemotherapy should be offered to elderly patients without exclusion from clinical

trials. Age should not influence the decision to offer adjuvant or palliative chemotherapy to older patients. Assessment of PS and weight loss should be used to guide decision making in difficult cases.

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