

Treatment response in elderly patients with advanced colorectal cancer at King Abdulaziz Medical City, Princess Norah Oncology Center, Jeddah

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ABSTRACT

Introduction: Colorectal carcinoma is the most evident carcinoma in the elderly. Despite its high incidence and mortality rate, there is insufficient research about the best treatment options for colorectal carcinoma. **Objective:** This study was designed to assess the best treatment modality for colorectal carcinoma in elderly Saudi patients. **Methods:** We conducted a retrospective analysis of medical records at the Princess Norah Oncology Center (PNOC), King Abdulaziz Medical City, Jeddah, Saudi Arabia. We included patients treated at PNOC between 2010 and 2015. Only patients aged above 70 years with advanced colon were included in the study. **Results:** The cohort included 57 patients with an average age of 76.51 with 27 alive patients and 30 dead patients. Nonmucinous adenocarcinoma had significant higher mortality ($n = 20$). Most patients received surgical treatment which was associated with less risk for mortality; however, it was nonsignificant. Surgery was followed by first-line treatment which had a mortality rate of 50%. The least treatment associated with mortality was local liver treatment ($n = 0$). Survival analysis found that only treatment with significant higher survival was shift to next line of treatment (at least once) [HR = 0.06, 95% CI (0.00, 0.79), P value = 0.03]. Other treatments were not associated with significant mortality reduction. First-line treatment was associated with higher mortality risk; nevertheless, it was nonsignificant. **Conclusion:** Local radiotherapy and local liver ablation had the least mortality rate. However, in multivariate Cox regression analysis, we found that shift to next line of treatment was associated with the significant high survival rate.

Keywords: Colorectal cancer, colorectal carcinoma, elderly, Saudi Arabia, survival rates

Introduction

Colorectal carcinoma is considered one of the most prevalent carcinomas in the whole world.^[1] In the USA, it is considered as the third cancer with highest mortality behind lung and prostate cancer. It is estimated that it is responsible for 49,190 cancer deaths with higher mortality in males than females.^[1] It

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was considered as a worldwide burden that affects the quality of life of the patients and their families.^[1] In Saudi Arabia, the incidence is much lower than the USA. In 1994, only 253 cases were reported; meanwhile, in 2010, 1033 cases were reported in 2010.^[2,3] However, since this increase was only limited to colorectal carcinoma and not to other cancers, it was not attributed to better reporting or registration.^[2] The mortality in Saudi Arabia was far less than the USA. The death rate decreased from colorectal carcinoma during the same period. However, the tripling number of cases during this period was mainly due to increase in the number of old age patients who were found to have higher risk of colorectal development.^[2] The increase is

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more apparent in age groups ranging from 65 to 68 years which was estimated to be twofold increase than other age groups. According to the worldwide statistics, this increase was more in male group than female group of the same age. Furthermore, a study found that the incidence in younger age groups was less than the older age group in Saudi Arabia.^[2,3]

The risk for colorectal carcinoma is multifactorial, including genetic, inflammatory conditions and environmental factors.^[1,4] It was found that sedentary life, obesity, old age, high-fat diet, and fiber-deficient diet were associated with higher risk of the cancer,^[5-10] and high-fat diet increased bile acids secretion so that colon bacteria work on these substances to convert them into toxic carcinogenic materials.^[9,11] Other risk factors included alcohol consumption and smoking. Smoking was found to increase the risk two to three folds as organs get rid of smoking toxins through its transport to colonic mucosa inducing mutagenesis and carcinogenesis.^[6,7]

In addition, the chronic inflammatory conditions like Crohn's disease and ulcerative colitis were associated with higher incidence of colorectal carcinoma.^[1] A study found that the ulcerative colitis was more associated with colorectal carcinoma than Crohn's disease and correlated with the duration of inflammatory conditions.^[12,13]

Other risk factors included hyperinsulinemia and special methods of cooking meat that were found to release toxic materials including carcinogenic heterocyclic amines and polycyclic aromatic hydrocarbons that were found to be toxic especially in the distal colon.^[9] Hyperinsulinemia was found to cause hyperproliferation of mucosal lining of the colon.^[10,14]

The genetic factors included both genetic and epigenetic factors that increased the incidence of colorectal carcinoma. HNF4A, CHDH1, and LAMB1 genes were found to increase the risk of colorectal carcinoma.^[14,15] Furthermore, single nucleotide polymorphisms were associated with higher mortality.^[15] The gene–environment interaction was clearly obvious in colorectal carcinoma. It was found obesity was associated with high risk of colorectal carcinoma and higher mortality rate in patients with CTNNB1-negative than patients with positive CTNNB1.^[10]

The treatment choice of colorectal carcinoma depends on its site, size, and age of the patients.^[16,17] Surgery was the treatment of options in many cases that can be done either through colonoscopy or through open, partial, or complete resection. However, the surgery is usually associated with low quality of life. Other treatment options included radiofrequency ablation and chemotherapy.^[16,17] Since most of colorectal carcinoma patients are old age and it was estimated that more than 60% of cases are older than 70, the treatment options in elderly always posed a challenge. The options range from total resection to palliative care.^[16,17] Millan *et al.* defined old age as “a progressive decline in the functional reserve of multiple organ systems; this process is highly individualized, and poorly reflected in chronological age.”^[16] Thus, the treatment options should be individualized for each patient.^[18] For instance,

old age was usually associated with worse surgical outcomes due to longer hospital stay and higher mortality,^[19] and patients older than the 80s had less survival rate by 15%.^[19,20] Postoperative complications were more prevalent in elderly which was explained by less tolerance to stressful events. Furthermore, elderly have two-to-three-fold increase in 6 months mortality rate.^[19,21]

The surgery modality choice in elderly posed further challenge, especially that there was low research available for this population. It has been noted that laparoscopic surgery is better than other modalities as it decreases postoperative complications.^[22-24] Moreover, it was not advised to do emergent surgery in case of perforation or sudden obstruction; it is better to do laparoscopic surgery after the study of the health status of the patients; then a decision will be made.^[21,25]

Another treatment option is chemotherapy. The poor function of kidney and liver, impaired bone marrow reserve, and impairment of vital organs increased the risk of toxicity from the chemotherapy.^[16-18,26] Other studies found that adjuvant therapy with chemotherapy was considered successful for stage II colorectal carcinoma in elderly.^[27-29] In the case of metastatic cancer, chemotherapy was also considered the best option; however, the results are not inconclusive.^[27,30,31]

The main limitation for the treatment of colorectal carcinoma in elderly is the lack of clinical trials and studies that assessed the efficacy of treatment options for this age group. Most participants in these studies are young adults. Furthermore, the research in Asian countries including Saudi Arabia is few and its results cannot be generalized.

That is why, this study was set out to stand on the treatment of choice in cases of advanced colorectal carcinoma in elderly.

Materials and Methods

Study setting

The study is a retrospective cohort study. The data were collected from the Medical Records Department at Princess Norah Oncology Center (PNOC), King Abdulaziz Medical City, Jeddah, Saudi Arabia.

Study subjects

All colonic adenocarcinoma patients treated at PNOC between 2010 and 2015 were considered. Only patients aged above 70 years with advanced colon cancer (stage IV) or unresectable early stage were included. The exclusion criteria were: patients with other malignancies in the last 5 years, patients undergoing neoadjuvant therapy, and patients at early stages (0–3).

Sampling and study design

This is a retrospective cohort study following a convenience sampling technique where all patients fitting the inclusion criteria were included.

Data collection and management

The information about colorectal carcinoma (CRC) patients was collected through structured data collection sheets. The medical records of patients admitted between January 2010 and December 2015 were used. The information was extracted using the electronic patient record systems (BEST CARE and Quadramed) and health records. Serial numbers were used instead of names to consider the confidentiality.

Ethical considerations

Research Ethical Committee approval was obtained prior to data collection from King Abdullah International Medical Research Center Research Committee, Ref# amr/RO/OM/2016/RC/115. Data were concealed with access granted only to investigators and security codes were given to every patient.

Statistical analysis

Descriptive statistics to summarize patients' characteristics were presented in the form of mean and standard deviation for continuous variables while categorical variables were presented in the form of frequency and percentage. Chi-square test (or Fisher's test, as appropriate) was used to compare between categorical variables, while Student's *t*-test (or Mann–Whitney test, as appropriate) was used to compare between the continuous variables. Kaplan–Meier analysis in the form of survival curves was used to present the survival probabilities of each group and a log-rank test was used to compare between their survivals.

A multivariate Cox regression analysis of overall survival was used to identify all possible prognostic factors affecting the survival of primary colorectal lymphoma (PCL) patients. Moreover, we computed the hazard ratios from the generated model coefficients to make it easily interpretable. All analyses were two-sided considering *P* value <0.05 as statistically significant and were conducted by using R version 3.2.5 software.

Results

Patient population and baseline characteristics

In our study, 57 patients were included who fulfilled the inclusion criteria. The mean age of included patients was 76.51 years. About 71.93% of the included patients were males. Of 57 patients in the cohort, 19 patients had recurrence. Nonmucinous carcinoma

represented 87.72% of the cases. Classification of patients into two groups based on mortality revealed that only the pathological type of cancer was associated with significant difference in survival [Table 1]. All cases of mortality were mainly due to nonmucinous adenocarcinoma (*n* = 20).

Treatment modalities for colorectal carcinoma in elderly

Comparison of mortality rate among different treatment options revealed that surgery had the highest mortality rate (*n* = 15); however, this difference was not significant. The second treatment option with highest mortality was first-line treatment and there was significant difference between those who received the treatment and other treatments (*n* = 10). The third treatment with high mortality was shifted to next line (*n* = 9) and it had significant higher mortality than other treatment options [Table 2]. The least treatment choices that were associated with less mortality were local liver ablation followed by local radiotherapy and third-line treatment. However, it was nonsignificant [Table 2].

The distribution of chemotherapy of first, second, and third lines among participants is illustrated in Figure 1. We found that in the first-line treatment, the highest number receiving capecitabine, irinotecan (CAPIRI) and bevacizumab followed by fluorouracil, leucovorin, oxaliplatin (FOLFOX) and bevacizumab [Figure 1]. For the second-line treatment, Leucovorin Calcium (Folinic Acid), Fluorouracil, Irinotecan Hydrochloride (FOLFIRI) and bevacizumab had the highest number patients receiving it followed by FOLFIRI and cetuximab. For the third-line treatment, capecitabene had the highest number of patients receiving it [Figure 1].

Overall survival

Based on multivariate Cox regression analysis, it was revealed that the first-line treatment was associated with less survival [Hazard Ratio (HR) =4.14, 95% confidence interval (CI) (0.31, 55.62)]; however, it was nonsignificant. Other treatment modalities were associated with less mortality; nevertheless, it was nonsignificant except for shift to next line of treatment (at least once) which showed significant decrease of the risk of mortality [HR = 0.06, 95% CI (0.00, 0.79), *P* value = 0.03] [Table 3].

Table 1: Basic characteristics of included patients

Outcomes	Alive		Dead		Total		P	
	n	%	n	%	n	%		
Age: Mean (SD)	75.41 (8.207)		78.55 (10.94)		76.51 (9.28)		0.269 ^Y	
Gender	Female	10	27.03	6	30.00	16	28.07	0.812
	Male	27	72.97	14	70.00	41	71.93	
Diagnosis	New diagnosis	25	67.57	13	65.00	38	66.67	0.844
	Recurrence	12	32.43	7	35.00	19	33.33	
Histological subtype	Mucinous adenocarcinoma	7	18.92	0	0.00	7	12.28	0.045 ^{*†}
	Nonmucinous adenocarcinoma	30	81.08	20	100.00	50	87.72	

SD: standard deviation; *Significant *P*<0.05; ^Y*t*-test; [†]Fisher's exact test

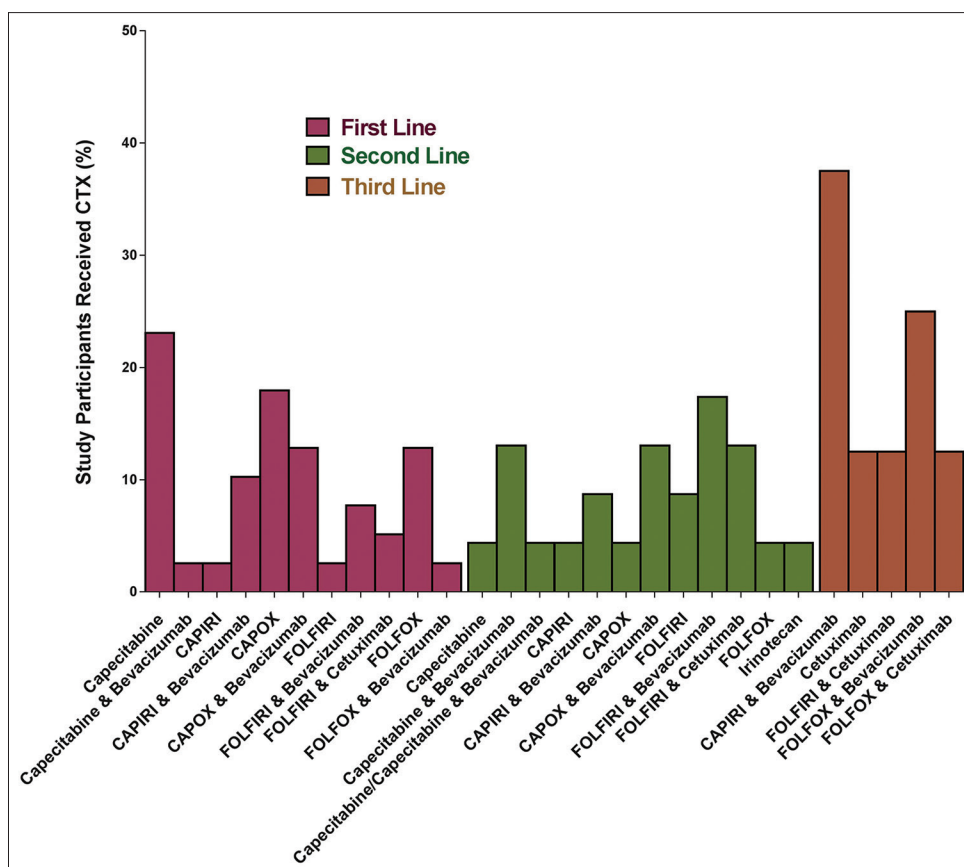


Figure 1: Distribution of different treatment regimens among patients who received chemotherapy

Outcome		Alive		Dead		Total		P
		n	%	n	%	n	%	
		Surgery	No	6	16.22	5	25	
	Yes	31	83.78	15	75	46	80.7	
First-line treatment	No	7	18.92	10	50	17	29.82	0.014* [†]
	Yes	30	81.08	10	50	40	70.18	
Second-line treatment	No	19	51.35	15	75	34	59.65	0.082
	Yes	18	48.65	5	25	23	40.35	
Third-line treatment	No	30	81.08	18	90	48	84.21	0.471 [†]
	Yes	7	18.92	2	10	9	15.79	
Local radiotherapy	No	31	83.78	19	95	50	87.72	
	Yes	6	16.21	1	5	7	12.28	
Local Liver ablation	No	33	89.19	20	100	53	92.98	0.705 [†]
	Yes	4	10.81	0	0	4	7.01	
Shift to next line of treatment (at least once)	No	7	18.92	11	55.00	18	31.58	0.005*
	Yes	30	81.08	9	45.00	39	68.42	

*Significant P<0.05; [†]Fisher's exact test

Discussion

This study was considered the first in Saudi Arabia to assess the treatment options in elderly population in advanced colorectal carcinoma. The cohort included 57 patients with average age of 76.51 years, where 27 were alive and 30 were dead. The only significant determining factor for mortality was the pathology of carcinoma. It was found that nonmucinous adenocarcinoma had

significant higher mortality ($n = 20$). Our main result was that most patients receive surgical treatment, which was associated with less risk for mortality; however, it was nonsignificant. Surgery was followed by first-line treatment, which had 50% mortality rate. Least treatment associated with mortality was local liver treatment ($n = 0$). Survival analysis found that the only treatment with significant higher survival was shifted to next line of treatment (at least once) [HR = 0.06, 95% CI (0.00, 0.79), P value = 0.03]. Other treatments were not associated with significant mortality reduction. First-line treatment was associated with higher mortality risk; nevertheless, it was nonsignificant.

Treatment options for colorectal carcinoma are limited in elderly. The elderly people are considered a special case for the treatment due to their poor health and impairment of vital organs. Furthermore, impaired response to stressful events made the choice of treatment difficult.^[16-18,20]

Surgical treatment of colorectal carcinoma is either open surgery or laparoscopic surgery. Based on clinical trials, laparoscopic surgery was associated with less mortality rate due to low risk of complications and shorter hospital stay.^[22] A study reported that it had overall survival of 85% compared to 81% of open surgery.^[23] Another study found that emergency surgery had less survival rate than elective surgery.^[21,25] Furthermore, a study compared between laparoscopic surgery and open surgery

Table 3: Multivariate Cox regression analyses of overall survival for different treatment modalities

Parameters	HR [95% confidence interval]	P
Surgery		
No	Reference	
Yes	0.28 [0.08, 1.06]	0.061
Local radiotherapy		
No	Reference	
Yes	0.12 [0.01, 1.05]	0.055
First-line treatment		
No	Reference	
Yes	4.14 [0.31, 55.62]	0.284
Second-line treatment		
No	Reference	
Yes	0.82 [0.17, 3.96]	0.810
Third-line treatment		
No	Reference	
Yes	0.91 [0.15, 5.51]	0.915
Shift to next line of treatment (at least once)		
No	Reference	
Yes	0.06 [0.00, 0.79]	0.033*

*Significant $P < 0.05$

had found that both treatments had the same outcome with no difference in survival.^[24] The results were consistent with another study that found both have good prognosis in colorectal carcinoma in elderly.^[22,24] The fact that surgery was associated with low mortality risk is consistent with our results. In addition, laparoscopic hepatectomy was found to be efficient for metastatic colorectal carcinoma and was associated with lower mortality.^[32]

A study found that chemotherapy is as effective in elderly as young adults.^[32] Furthermore, both groups dealt with side effects and complication well. Combination therapy in elderly had confusing results. A study, which compared FOLFOX as adjuvant treatment, found that it had worse outcome in elderly with hematological toxicity.^[33,34] Our study found that first-line treatment had worse survival. Other studies, which assessed the use of FOLFIRI in elderly patients, revealed that only 35% of patients recovered.^[29] Furthermore, they found that overall survival ranged from 15.3 to 14.5 months.^[29] Souglakos *et al.* reported that 3.3% died due to toxic effect.^[29] Many trials assessed the efficacy of capecitabine with adjuvant treatment of colorectal carcinoma in elderly.^[27,30,35-37] A study found that capecitabine had the least toxicity and side effects when combined with oxaliplatin.^[30,37] Furthermore, another study found that it achieved with highest overall survival of 2 years when combined with neoadjuvant treatment and oxaliplatin.^[36] However, other studies reported controversial results regarding its efficacy.^[36,37]

A systematic review found that first-line monotherapy was considered the best option for elderly which is contradicting to our study.^[26]

Generally, combination chemotherapy was found to have favorable outcome in colorectal carcinoma in elderly.

In addition, in our study, local radiotherapy had the lowest mortality. Many studies supported the fact that the local radiotherapy had good outcome in elderly patients.^[26,38] However, full assessment of the health of elderly patients is needed for the best outcome to be obtained during local radiotherapy.

Conclusion

Based on our study of surgical treatment, second- and third-line treatments were not associated with high mortality risk. The highest mortality risk was in first-line treatment. Meanwhile, shift to next line of treatment was associated with the highest survival rate. In addition to clearer and more accurate information about their disease, patients also need better guidance about “where to go” after their disease is diagnosed and consulting first by their primary-care physician.^[39]

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Conflicts of interest

There are no conflicts of interest.

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