

## Chemotherapy Compliance and Tolerance in Elderly and Non-Elderly Patients with Colorectal Cancer: A Single Institution Study

Norly Salleh<sup>1\*</sup>, Amirah Yusof<sup>1</sup>, Mohd Aizat Hamdan<sup>1</sup>, Robi'ah Al-Adawiyah Sadarman<sup>1</sup>, Shamsiah Mohd Noor<sup>1</sup>  
<sup>1</sup>Pusat Rawatan Onkologi Yayasan, Hospital Pakar Sultanah Fatimah Muar, Jalan Salleh, 84000 Muar, Johor, Malaysia

\*Corresponding author: Norly Salleh

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**Abstract:** The objectives of this retrospective, observational study are to compare the compliance and tolerance rate between elderly and non-elderly patients with colorectal cancer, and to ascertain the stage at presentation. All adult patients with diagnosis colorectal cancer who received first line chemotherapy (adjuvant or palliative) between January 2017-January 2019 were included. Data on demographic, clinic-pathological, treatment and patient outcome were collected. Toxicity data was collected as they appear. These data were then analyzed using IBM®SPSS® Statistics Version 24. Sixty-four patients were included. There were almost equal numbers of elderly and non-elderly patients. Thirty-five patients were Malay (54.7%), Chinese 26 (40.6%) and Indian 3 (4.7%). Their age ranges from 38-82 years old. Most patients received FOLFOX regimen (73.4%), followed by Mayo regimen and capecitabine (10.9% each). There was no significance difference in the type of chemotherapy and number of cycles given. The majority received combination therapy rather than single therapy. There was no difference in the terms of toxicity between the study populations. Thirty-three percent of elderly and thirty-five percent of non-elderly patients had no documented chemotherapy. The most common toxicity is neutropenia, followed by thrombocytopenia and anaemia. In total, 25% (16 patients) did not complete their chemotherapy for various reasons. Nine were elderly patients (56.3%). Presentation at Stage 3 and 4 accounted for 70.3% (45 patients) of the study population. Elderly colorectal cancer patients' should be treated with equal therapeutic opportunities as their younger counterparts. Biological age should be considered when deciding treatment regime rather than chronological age.

**Keywords:** Chemotherapy, colorectal cancer, elderly, toxicity, stage, compliance, tolerance.

### INTRODUCTION

Colorectal cancer (CRC) has a prevalence of 13.2 percent in Malaysia (MOH Malaysia, 2015) and it is expected to be on the rise due to the increasing rate of obesity. Another risk factor of CRC is age. Old age and carcinogenesis has been shown to have association for most cancer types. According to Malaysian National Cancer Patient Registry – Colorectal Cancer (2008-2013) the mean age for CRC patients was 61.6 years old (standard deviation of 12.7) (MOH Malaysia, 2014). Conventionally, 'elderly' has been defined as a chronological age of 65 years and above. Most of the published studies in oncology use the cut-off of 65 or 70 years old. However, the population in Malaysia is considered relatively young as compared to the developed nation. In Malaysia, the average life expectancy is 73.2 years for male and 77.6 for female (WHO, 2018). Therefore, in Malaysian context, elderly patients are defined as age more than 60 years old, which is the definition used for this study.

The mainstay of treatment for CRC is surgical resection, which offers the best hope for cure. Chemotherapy and radiotherapy are used to downstage the tumour, as adjuvant therapy and for palliative purposes. Chemotherapy is associated with a lot of side effects and these side effects can be devastating especially to an elderly and frail cancer patients. There is a tendency to prescribe elderly patients with chemotherapy of suboptimal intensity and duration, mainly due to the fears of poor compliance and excessive toxicity. A study by Bakogeorgos in 2013 have shown that despite the inferior type and intensity of chemotherapy, elderly patients derived equivalent benefit to their younger counterparts and hence they support the use of optimal chemotherapy in elderly patients with metastatic CRC (Bakogeorgos M et al., 2013). This study is done to assess and compare our local elderly and non-elderly patients chemotherapy compliance and toxicity issues. Toxicity will be evaluated according to the National Cancer Institute

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Common Toxicity Criteria, version 5 (National Cancer Institute Common Toxicity Criteria).

Hospital Pakar Sultanah Fatimah (HPSF) Muar is a district hospital in the state of Johor, Malaysia. There are 550 gazetted beds in the hospital. The department of surgery serves general surgical services as well as oncology services. Since 2011 we have been treating 1079 oncology patients. Our patients mostly come from district Muar, Segamat and Tangkak. However there are some patients from other states mainly southern Pahang and Negeri Sembilan. In the year 2012 alone, 649 patients had undergone chemotherapy in our hospital.

In Malaysia, there is a shortage of oncologists and there are only 6 existing Radiotherapy and Oncology Centers (RTOC) within the Ministry of Health, Malaysia. Because of this the National Strategic Plan for Cancer Control Programme 2016-2020 proposed the development of clinical oncology unit (COU) in tertiary hospitals. A specialist who has an interest and is involved in cancer management will head the COUs. The regional oncologists visit the clinics periodically at least once a month. HPSF Muar was chosen as one of the COUs and with the help Yayasan Kanser Tunku Laksamana Johor (YKTLJ), Pusat Rawatan Onkologi Yayasan (PROY) was established. The unit was the idea of our Queen of Johor, Her Majesty Raja Zarith Sofiah binti Al-Marhum Sultan Idris Shah. PROY was officially launched by the queen herself on 28 March 2017. All day care chemotherapy patients are treated in the unit. The unit also accepts any patients who walk in with any cancer related issues.

### Objective

1. To compare compliance and tolerance between elderly and non-elderly patients with colorectal cancer
2. To ascertain the stage of CRC in our study population

## MATERIALS AND METHODS

This is a retrospective, observational study conducted at the Department of Surgery and Oncology Unit of Hospital Pakar Sultanah Fatimah Muar, Johor. Census data from Cancer Registry for subjects fulfilling inclusion and exclusion criteria were recruited as samples for the study. Subjects are all adult patients who with the diagnosis of colorectal cancer who received first line chemotherapy (adjuvant or palliative) between January 2017 until January 2019. All patients with incomplete data were excluded. Data on demographic, clinic-pathological, treatment (chemotherapy regime, duration) and patient outcome were collected and analysed. Toxicity data was collected as they appear. If patient already has some symptoms prior to starting the chemotherapy, toxicity was defined as worsening of the symptoms. Onset of symptoms of toxicity was taken as anytime from starting the chemotherapy until 6 weeks after completing the chemotherapy. These data were then analyzed using IBM®SPSS® Statistics Version 24.

### Ethics

This study has been approved by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia.

## RESULTS

### Clinical and Pathological Characteristics

From January 2017 until January 2019, there were 64 patients who fit our inclusion and exclusion criteria and included in the study. We have almost equal number of elderly and non-elderly patients in our colorectal cancer study population. Their races are as follows: Malay 35 patients (54.7%), Chinese 26 (40.6%) and Indian 3 (4.7%). Their age ranges from 38-82 years old. Thirty-three patients (51.6%) were aged 60 and above. Clinical and pathological characteristics of the study population are presented in Table 1. There was no significance difference between the two groups. The most common site for cancer was the rectum, followed by sigmoid and transverse colon.

**Table-1: Clinical and pathological characteristics of the study population**

Characteristics	Total N (%)	Elderly N (%)	Non-elderly N (%)	p-value (2-sided)
<b>Age (years)</b>				
Mean	59.4 ± 10.2	67.6 ± 5.6	50.6 ± 5.6	
Median	60	66	52	
<b>Gender</b>				
Male	39 (60.9)	23 (35.9)	16 (25.0)	2.196
Female	25 (39.1)	10 (15.6)	15 (23.4)	
<b>Location</b>				
Caecum	2 (3.1)	1 (1.6)	1 (1.6)	0.980
Ascending	2 (3.1)	1 (1.6)	1 (1.6)	
Transverse	10 (15.6)	4 (6.3)	6 (9.4)	
Descending	2 (3.1)	1 (1.6)	1 (1.6)	
Sigmoid	20 (31.3)	11 (17.2)	9 (14.1)	
Rectum	23 (35.9)	13 (20.3)	10 (15.6)	
Rectosigmoid	5 (7.8)	2 (3.1)	3 (4.7)	

### Co-Morbidity

Thirteen patients had diabetes mellitus (20.3%), twenty hypertension (31.3%), three ischaemic heart disease (4.7%), twelve hypercholesterolaemia

(18.7%) and sixteen had other pre-morbid conditions (25%). Although more elderly patients have co-morbidities, there were not statistically significant (Table -2).

**Table-2: Co-morbidity of the study population**

Pre-morbid	Total N (%)	Elderly N (%)	Non-elderly N (%)	p-value (2-sided)
Diabetes Mellitus	12 (18.8)	9 (14.1)	4 (6.3)	0.153
Hypertension	20 (31.3)	13 (20.3)	7 (10.9)	0.147
Hypercholesterolaemia	3 (4.7)	3 (4.7)	0 (0)	0.086
Ischaemic Heart Disease	11 (17.2)	7 (10.9)	4 (6.3)	0.415
Others	16 (25.0)	11 (17.2)	5 (7.8)	0.112

### Treatment Regimen

In general, most patients received FOLFOX regimen chemotherapy (73.4%), followed by Mayo regimen and capecitabine (10.9% each). There was no significance difference in the type of chemotherapy regime given to either population. The majority received combination therapy rather than single therapy. There was also no difference in the terms of

number of cycles given to each group. Most of our study population presented with stage 3 or 4 colorectal cancers (Figure 1). For elderly patients with metastatic colon cancer, FOLFOX has been shown to be the best first-line therapy {Idrees M et al, 2019}. Surgery was performed in more than 75% of the study population and almost 76% of the elderly were operated on.

**Table-3: Treatment regimen**

Characteristics	Total N (%)	Elderly N (%)	Non-elderly N (%)	p-value (2-sided)
<b>Chemo Regime</b>				
5-FU Alone	6 (9.4)	3 (4.7)	3 (4.7)	0.936
Capecitabine Alone	7 (10.9)	4 (6.3)	3 (4.7)	0.625
Mayo	7 (10.9)	4 (6.3)	3 (4.7)	0.754
DeGrammont's	3 (4.7)	3 (4.7)	0 (0)	0.086
FOLFOX	47 (73.4)	23 (35.9)	24 (37.5)	0.485
FOLFIRI	1 (1.6)	1 (4.7)	0 (0)	0.329
XELOX	3 (4.7)	1 (4.7)	2 (3.1)	0.518
XELIRI	0 (0)	0 (0)	0 (0)	-
Others	1 (1.6)	1 (4.7)	0 (0)	0.329
<b>Targeted Therapy</b>	0 (0)	0 (0)	0 (0)	-
<b>Surgery</b>	48 (75.0)	25 (75.8)	23 (74.2)	0.625

### Tolerance and Compliance

There was no significance difference in terms of toxicity between the study populations (Table-4). Thirty-three percent of elderly and thirty-five percent of non-elderly patients had no documented chemo-

toxicity. The most common toxicity is neutropenia, followed by thrombocytopenia, anaemia, diarrhoea and peripheral neuropathy. None of the patients had documented mucositis.

**Table-4: Toxicity data**

Toxicity	Total N (%)	Elderly N (%)	Non-Elderly N (%)	p-value (2-sided)
Neutropenia	34 (53.1)	17 (26.6)	17 (26.6)	0.790
Anaemia	7 (10.9)	3 (4.7)	4 (6.3)	0.625
Thrombocytopenia	13 (20.3)	5 (7.8)	8 (12.5)	0.290
Peripheral neuropathy	2 (3.1)	0 (0)	2 (3.1)	0.138
Diarrhoea	4 (6.3)	2 (3.1)	2 (3.1)	0.949
Mucositis	0 (0)	0 (0)	0 (0)	-

For patients who developed neutropenia (53.1%), there were almost equal numbers of elderly and non-elderly patients (Table-4). Most of them had grade 1 neutropenia. This trend is seen in all types of

toxicity where there is almost equal number of elderly and non-elderly patients who developed the toxicity. The majority developed low-grade toxicity.

**Table-5: Grade of Toxicity**

	Grade 1		Grade 2		Grade 3		Total	p-value
	Elderly	Non-elderly	Elderly	Non-elderly	Elderly	Non-elderly		
Neutropenia	11	12	5	3	1	2	34	0.814
Thrombocytopenia	4	6	1	2	0	0	13	0.559
Anaemia	3	2	0	1	0	1	7	0.513
Peripheral Neuropathy	0	2	0	0	0	0	2	0.138
Diarrhoea	1	1	0	1	1	0	4	0.571
<b>Total</b>	19	23	6	7	2	3		

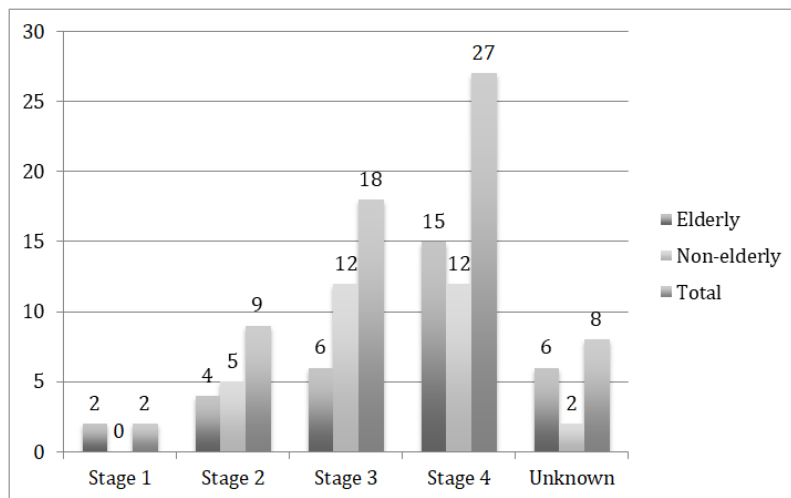
In total, 25% (16 patients) did not complete their chemotherapy regimen for various reasons. Out of this, nine were elderly patients (56.3%). Three of them voluntarily withdrew from treatment; three had change of chemotherapy regimen due to disease progression and three died during treatment. In non-elderly group, seven (43.8%) did not complete their treatment. One withdrew from treatment; three had change of regimen due to disease progression and three died.

**Stage at Presentation of Patients**

As mentioned earlier, most of our patient presented late with Stage 3 and 4 accounting for 70.3% (45 patients) of the study population. This is a challenge for us as prognosis is related to the stage of the disease with 5-year survival rate for localized cancer is 90.2% (7). This percentage dropped to 14.3% if the cancer has metastasized {NCI: SEER}.

**Table 6: Staging and Site of Metastasis**

Characteristics	Total N (%)	Elderly N (%)	Non-elderly N (%)	p-value (2-sided)
<b>Initial Stage</b>				
I	2 (3.1)	2 (3.1)	0 (0)	0.157
II				
IIA	6 (9.4)	2 (3.1)	4 (6.3)	
IIB	2 (3.1)	2 (3.1)	0 (0)	
IIC	1 (1.6)	0 (0)	1 (1.6)	
III				
IIIA	8 (12.5)	3 (4.7)	5 (7.8)	
IIIB	7 (10.9)	3 (4.7)	4 (6.3)	
IIIC	3 (4.7)	0 (0)	3 (4.7)	
IV				
IVA	17 (26.6)	11 (17.2)	6 (9.4)	
IVB	10 (15.6)	4 (6.3)	6 (9.4)	
IVC	-	-	-	
Unknown	8 (12.5)	6 (9.4)	2 (3.1)	
<b>Site of Metastasis</b>				
Liver	15 (23.4)	8 (1.3)	7 (10.9)	0.580
Lung	17 (26.6)	10 (15.6)	7 (10.9)	0.485
Brain	1 (1.6)	1 (1.6)	0 (0)	0.329
Bone	3 (4.7)	2 (3.1)	1 (1.6)	0.592



**Figure-1: Stage at Presentation of Patients with Colorectal Cancer (Chi Square Test p = 0.172)**

## DISCUSSIONS

There is a possibility of overuse of chemotherapy among younger adults with colon cancer. Young and middle age adults are more likely to receive postoperative systemic chemotherapy compared with older patients across all tumour stages (Manjelievskaia J *et al.*, 2017). Both groups were more likely to receive multi-agent chemotherapy than were older patients. However, this is not true for our study population. There is no significant difference in terms of types of chemotherapy and the number of cycles given to each group. One reason for this could be because the majority of our patients presented at a late stage. So the likelihood of them getting multi-agent chemotherapy and a longer chemotherapy cycles are higher. In terms of toxicity, Begg *et al.*, found that in general, the elderly patients have identical rates of severe toxicity as their younger counterparts (Begg CB *et al.*, 1983). We found similar findings in our study population. Some authors found that elderly patients do not experience a higher rate of toxicity than younger patients if doses are adjusted to renal function (Kimmick GG *et al.*, 1997).

Seventy five percent of our patients completed their chemotherapy as planned. More than half of those who did not complete their chemotherapy treatment were elderly (56.3%). Among the reasons for non-completion of the therapy are voluntary withdrawal from treatment, change of regime due to disease progression and death. Mari *et al* reported compliance rate of 56% in their multicenter research on compliance to chemotherapy after rectal surgery (Mari GM *et al.*, 2019). Xu *et al.*, found an even lower compliance rate at only 32% in their study of rate of adjuvant chemotherapy in patients with stage II and III rectal cancer (Xu Z *et al.*, 2017). We found that the reason why our population seems to have a high compliance rate is because we counted the patients who completed their chemotherapy regimen even after they had defaulted a few months, as long as they completed the regime. Had we taken these patients out, our compliance rate would have been lower.

Late presentation of cancer to the health care provider is not a new issue in the Malaysian setting. The lack of trust in health care professional, especially when it comes to needing to undergo a surgery or chemotherapy, is still somewhat thick in the heart of Malaysians especially among the elderly and the underprivileged group. This is disheartening as mortality due to colorectal cancer can be effectively reduced with early diagnosis and treatment. Another reason why our population presented late is the lack of national screening program. In Malaysia, colorectal cancer is the second most common cancer in both males and females. A national screening program would help to reduce the economic burden of managing colorectal cancer in the long term.

There are a lot of considerations that need to be taken by the oncologists before starting chemotherapy treatment for colorectal cancer patients, especially if the patient is an elderly. Other than stage of the disease and histo-pathological result, they also need to consider patient's premorbid conditions, concurrent medications, functional status, as well as social support network of the patient. That is why there is a worry that we may be undertreating our elderly colorectal cancer patients. However from the data that we have gathered from this study, this is not an issue in our institution. Fitness for chemotherapy should not be defined by age alone, as a lot of other factors need to be taken into account to determine someone's fitness. Biological age should be considered when deciding treatment regime rather than chronological age. Some authors advocated that decisions making in elderly patients should be based on the results of a geriatric assessment (Wedding U *et al.*, 2007, Kohne C. H *et al.*, 2008). Patients with few or no limitations should be treated as younger patients are treated.

## CONCLUSIONS

Elderly colorectal cancer patients' should be treated with equal therapeutic opportunities as their younger counterparts. Biological age should be considered when deciding treatment regime rather than chronological age.

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**Conflict of Interest:** This study has no conflict of interest.

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