Original Article

Male patients commencing FOLFOX/ FOLFIRI chemotherapy in 2014, descriptive statistics

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Abstract

Background: Metastatic colorectal cancer is an incurable illness; however the advent of chemotherapy has significantly improved survival and symptom control. FOLFOX and FOLFIRI are used at SPBOH as the standard of care for patients with metastatic disease. No statistical data is available on that cohort of patients; this study aims to establish a population data-set for patients on FOLFOX/FOLFIRI.

Methods: This retrospective cross-sectional study included all patients on FOLFOX and FOLFIRI in 2014. Only male patients were included, data was retrospectively extracted from the ward's logbook and ISOFT clinical manager. Cycle 1, 6 and 12 dates were documented. Data was analysed using clinically reliable statistical tools, all reported *p-values* were statistically significant at *<0.05*.

Results: From a total of 108 patients, 4 patients were excluded from the analysis. The average age of patients was 65.2 years. The average length of 12 cycles was 24.5 weeks. 19% of patients had cycles longer than 7 months whereas only 10% lasted more than 8 months on treatment. 41% of patients dropped out before completing the full course with a complication and mortality rate of 17%. Patients on FOLFIRI were more likely to have their chemotherapy changed and were also more likely to have received previous treatment.

Conclusion: Although chemotherapy increases survival in metastatic colorectal cancer we have to appreciate that many patients do not proceed smoothly with their treatment. Many of those patients are middle aged independent individuals, after-all the physician must draw the line at the appropriate time and focus on palliative care rather than continuing ineffectively with chemotherapy.

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Introduction

With a global incidence of 1.2 million cases annually, colorectal cancer stands as one of the most common and lethal malignancies. It is the fourth most common cause of death in men and the third in women, killing an estimate of 608,700 patients each year.[1] In the developed world, death rate from colorectal cancer has been decreasing, mainly due to screening and the detection and treatment of early stage disease. Population based screening programmes are usually not affordable in many parts of the world because of the expense of colonoscopy.[2] Loco-regional data is lacking, however in the United States, around 2/5 of colorectal cancer patients present with stage I and II local disease, around 2/5 with regionally advanced stage III disease and 1/5 with metastases.[3]

Metastatic colorectal cancer is an incurable illness, however in the advent of chemotherapy survival and symptom relief has significantly improved. Chemotherapy for metastatic colorectal cancer has developed in a stepwise fashion over the past decades. 5-FU was the first chemotherapeutic agent shown to be effective. Subsequently the regimen of 5- FU/cisplatin/folinic acid, was shown to increase survival in metastatic colorectal cancer from 5 to 11 months.[4] More so two cytotoxic chemotherapies exhibited considerable efficacy when added to the 5-FU/folinic acid backbone. It is

combined with Oxaliplatin in the FOLFOX infusional regimen and with Irinotecan in the FOLFIRI regimen. Multiple clinical trials have shown that the FOLFIRI and FOLFOX regimens are equivalent in terms of efficacy. For first line therapy, oncologists typically choose between FOLFOX and FOLFIRI based on the side effect profile of both regimens.[5-6]

To prolong survival and improve quality of life, palliative chemotherapy is administered to patients with locally advanced or metastatic cancer. As a result of this established benefit, the 1990 National Institutes of Health Consensus Panel on Colorectal Cancer recommended routine 5-FU-based adjuvant chemotherapy for patients with node-positive (stage-III) colon cancer. This was originally recommended for 12 months, and later on revised to 6 months because of proven equivalence in survival benefits. [7- 9]

As the only provider of systemic chemotherapy treatment in Malta, Sir Paul Boffa Oncology Hospital (SPBOH) serves the whole population of Malta and Gozo and caters for a wide array of cancer patients. FOLFOX and FOLFIRI are used at SPBOH as the standard of care for patients with metastatic as well as adjuvant colorectal cancer treatment. It is important to note that the initiation of adjuvant/palliative chemotherapy is just the first step in survival improvement. Because the completion of chemotherapy is associated with increased survival, it is essential to complete the chemotherapy cycles once initiated.[7] Little is known about the actual completion rate of such a therapy in our community, and we were unable to identify other regional studies that assessed the completion of chemotherapy for colorectal cancer in actual practice. This study aims to form a population-based assessment for patients who were started on FOLFOX and FOLFIRI.

Methods

This retrospective cross-sectional study was done at Sir Paul Boffa Oncology Hospital. SPBOH is the only provider of systemic chemotherapy treatment in Malta. It serves the whole population of Malta and Gozo and hosts a wide array of cancer patients. Permission was granted by foundation school audit and quality Improvement committee, Malta. All male patients who were started on FOLFOX or FOLFIRI in 2014 were included in the study. Data consisting of the patient's age, chemotherapy type and cycle, frequency of admission, tumour type and mortality were retrospectively extracted from the ward's logbook, computer registry and ISOFT clinical manager. The patients' admission dates for cycles 1, 6 and 12 dates were documented. A full course of modified de Gramont FOLFOX or FOLFIRI chemotherapy consists of a total of 12 cycles administered every fortnight. All patients who were intended to complete 12 cycles of adjuvant or palliative chemotherapy were included in the analysis. Patients who were on neo-adjuvant treatment and patients on maintenance chemotherapy for more than 12 months were excluded. Data was analysed using SPSS statistical tool. We first described the characteristics of all study cases and then used chi-square tests to compare the initiation and completion rates of adjuvant chemotherapy by characteristics. Multiple logistic regression was used to identify factors associated with the initiation and completion of chemotherapy. All reported *P-values* were two sided and were considered to be statistically significant at less than *0.05* levels.

Results

During 2014 SPBOH had a total of 1350 male admissions for chemotherapy, 874 of those admissions were for the infusion of either FOLFOX or FOLFIRI, 647 and 227 respectively. During this period a total of 108 patients were newly started on either treatment. Only patients who were on FOLFOX or FOLFIRI were included. Four patients were excluded from the analysis because they were on neo-adjuvant therapy or maintenance chemotherapy for more than 12 cycles.

The average age of patients was 65.2 years (ranging from 31-82) (64-67 95% confidence interval). 83% of patients were < = 70 years old. The main bulks, 65 patients, were between the ages of 60-70 years. Only 17 patients were > 70 years old. *(Table 1, 2) (Graph 1)*

***Table 1**: Age statistics*

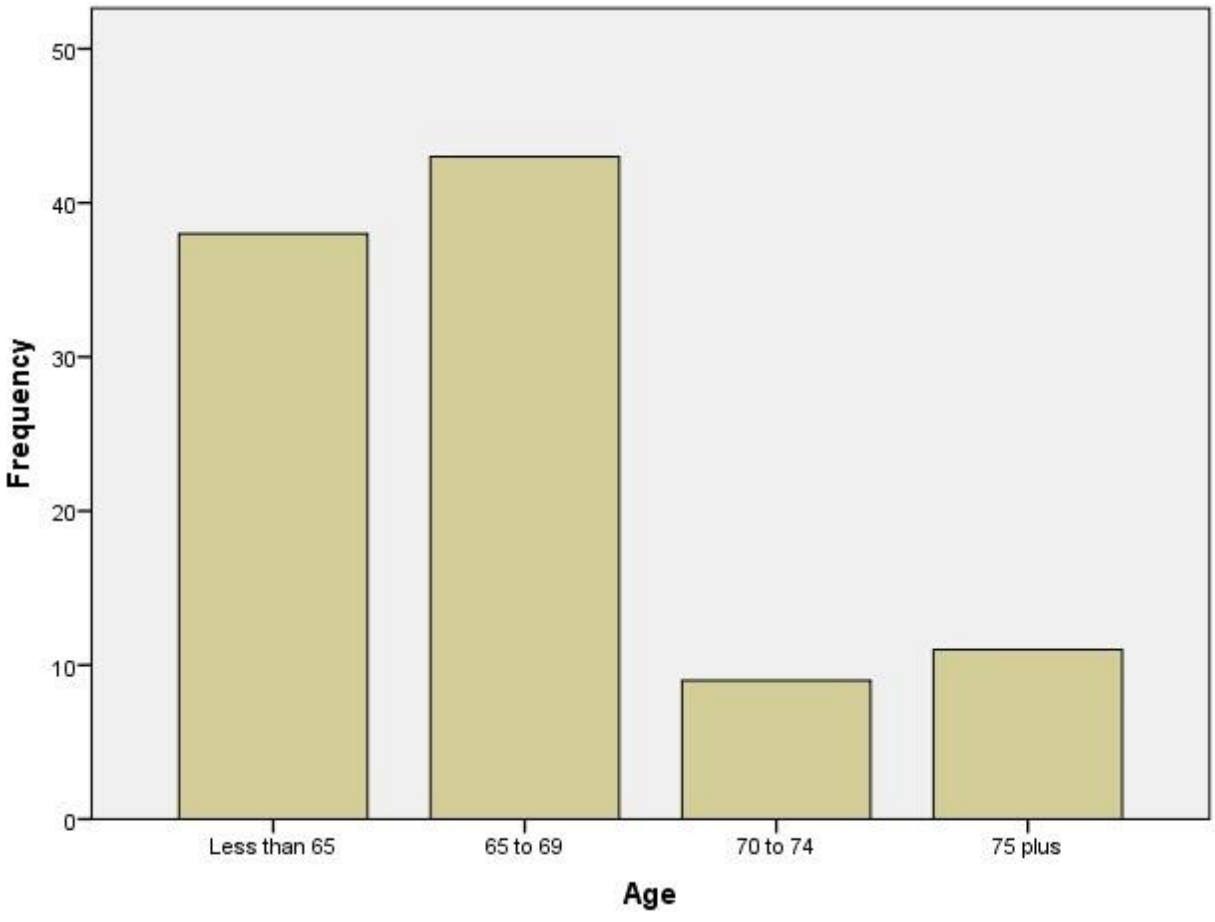
		Age	
	Mean Difference	95% Confidence Interval of the Difference	
		Lower	Upper
age	65.198	63.63	66.77

Mean	65.20
Median	67.00
Mode	67
Std. Deviation	7.942
Minimum	31
Maximum	82

***Table 2**: Age statistics*

Years	Frequency
Less than 65	38
65 to 69	43
70 to 74	9
75 plus	11
Total	101

***Figure 1**: Age Distribution*



88 patients were on FOLFOX and 16 on FOLFIRI. Of those 12 patients had upper GI primary malignancies, 88 had lower GI malignancies and only 3 had other types.

91 patients did not receive previous treatments, 6 were previously treated with FOLFOX, 3 with FOLFIRI and 4 received other kinds of treatment. 89 patients (82%) did not have a change in Chemotherapy during the 12 cycles. However, the treatments of 14 patients (13%) were altered; 5 patients were changed to FOLFOX, 7 changed to FOLFIRI and 3 were changed to other treatment regimens.

43.8% (*n*=7) of patients on FOLFIRI had their chemotherapy changed whereas only 9.1% (*n*=8) of patients on FOLFOX had a change in treatment. Patients on FOLFIRI were more likely to have their chemotherapy changed x^2 (1) = 13.176, *p<0.001*. *(Table 3)*

***Table 3**: Chemotherapy regimen and whether or not it was changed*

			Chemotherapy changed		Total
			Yes	No	
Chemotherapy Regimen	FOLFOX	Count	8	80	88
		% within Chemotherapy Regimen	9.1%	90.9%	100.0%
	FOLFIRI	Count	7	9	16
		% within Chemotherapy Regimen	43.8%	56.2%	100.0%
Total		Count	15	89	104
		% within Chemotherapy Regimen	14.4%	85.6%	100.0%

Patients on FOLFIRI were also more likely to have received previous treatment x^2 (1) = 24.312, *p<0.05*. Only 5.7% (*n*=5) of patients on FOLFOX received previous treatment; whereas 50% (*n*=8) of patients on FOLFIRI received previous treatment. *(Table 4)* Nonetheless, no statistically significant correlation between the types of chemotherapy and whether the patient will complete his chemotherapy cycles were found.

The average length of 12 cycles was 171.5 days or 24.5 weeks. The average length of cycles 1-6 and 6-12 were 11.6 and 12.9 weeks respectively. The mean difference between cycles 1-6 and cycles 6-12 is 1.6 weeks (1-2.3 95% confidence interval). 19% (*N=20*) of patients had cycles longer than 7 months whereas only 10% (*N*=11) lasted more than 8 months on treatment.

14.5% of patients (*N*=15) dropped out before completing 6 cycles, and 27% (*N*=28) of patients before finishing the full course. Therefore only 59% (*N*=61) continued for the whole 12 cycles. *(Graph 2)*

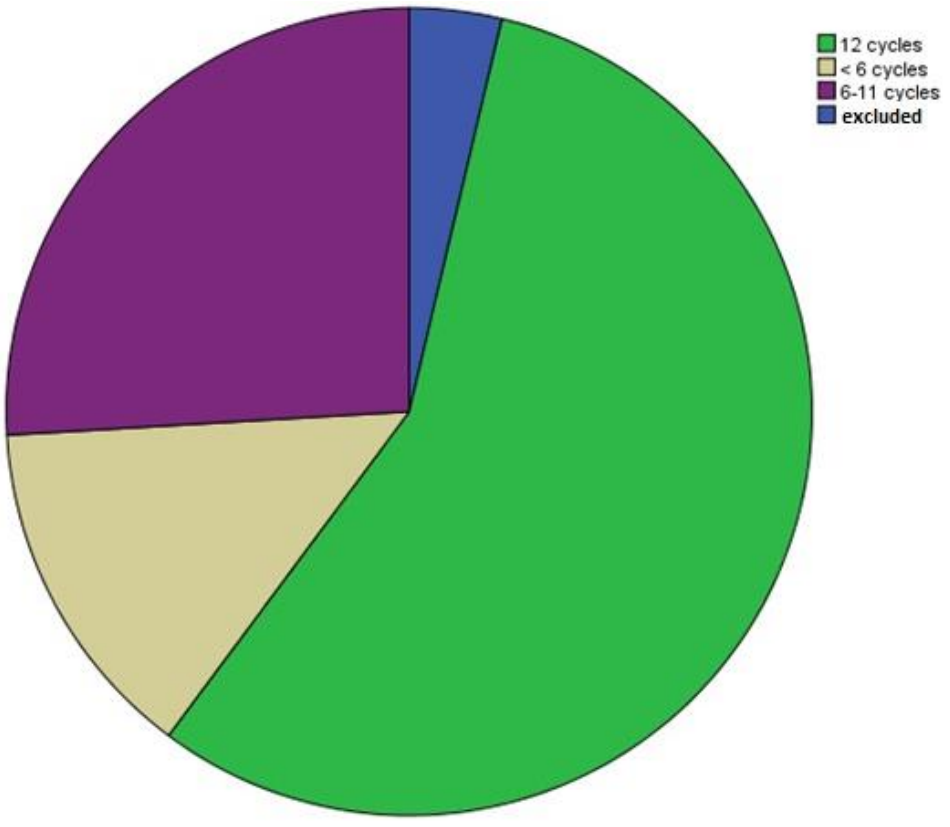
No statistically significant correlation was found between whether patients will complete chemotherapy and the presence of previous treatment, the type of chemotherapy, the presence of previous treatment, the primary tumour site or the age of the patients.

10 patients passed away before completing their planned chemotherapy cycles, 8 patients had significant thrombotic complications like deep venous thrombosis, pulmonary embolism and arterial embolism. Most complications occurred before finishing 6 cycles. Treatment was discontinued for the rest of the patients mainly because of poor response to chemotherapy and disease progression.

Table 4: *Chemotherapy regimen and presence of previous treatment*

			Previous treatment		Total
			FOLFOX/ FOLRIRI or OTHER	NONE	
CHEMO	FOLFOX	Count	5	83	88
		% within CHEMO	5.7%	94.3%	100.0%
	FOLFIRI	Count	8	8	16
		% within CHEMO	50.0%	50.0%	100.0%
Total		Count	13	91	104
		% within CHEMO	12.5%	87.5%	100.0%

Figure 2*: Number of chemotherapy cycles*



Discussion

This study provides a national overview for the use of FOLFOX/ FOLFIRI amongst Maltese patients with colorectal cancer and the proportion of patients who complete the prescribed therapy. The average age for patients in our study was 65.2; we had a significantly lower proportion of patients older than 70 years than those younger. These findings contradict with the natural prevalence of the disease, as colon cancer is predominantly a disease of the elderly population with an expected increase in prevalence with age [11]; nonetheless this may be explained by the patients and oncologists choice and preferences for a less aggressive approach to palliative care among the elderly; however, data were not available to statistically test these assumptions.

Physicians may be reluctant to endorse such aggressive therapy for elderly because of the uncertainties regarding the risk–benefit trade-offs. However this is not consistent with best practice guidelines, as neither guideline recommends age as a factor to consider in treatment decisions.[12] Moreover in our study elderly patients (>75) were as likely to complete the course of treatment as the younger patients.

The overall rate of treatment completion in our study was 59% (*N=61*). This equilibrates with those found in other international studies. One prospective study conducted in Houston Texas in 2011 found that overall completion rate of adjuvant chemotherapy among patients with colon cancer was 62.2%. Patient's age at diagnosis, comorbidity score and marital status were significantly associated with the rate of initiation and completion of adjuvant chemotherapy. [7]

Take gastro-oesophageal cancer as an example, a recent study found that the overall rate of treatment completion was 52.7% and ranged from 50–60% for patients with good performance status but was under 35% for patients aged 55 years or older with poor performance status. Treatment completion was not associated with site of cancer, pre-treatment stage, sex, comorbidities or histology. Likewise, rates of adjuvant chemotherapy in patients with epithelial ovarian cancer approximate 46.5%; age and more than two comorbidities were identified as significant predictors.[13] Our finding showed that no significant correlation was found between whether patients will complete chemotherapy and the presence of previous treatment or the primary tumour site and is consistent with previous research.

FOLFOX and FOLFIRI are the most commonly used infusion treatments at SPBOH comprising of around 70% of all chemotherapies administered in the hospital. The average duration of cycles is satisfactory with around 70% finishing within 24 weeks. Although underrepresented in our study sample, patients on FOLFIRI were much more likely to have been given previous treatments and have their chemotherapy changed. Nonetheless both regimens had equal completion rates with no statistically significant difference between them.

From our whole sample it is noted that only 16 patients were started on FOLFIRI whereas all the rest were on FOLFOX. This could explain the higher initiation rates for FOLFOX or a likely more tolerable side effect profile. Nonetheless FOLFOX can cause significant peripheral neuropathy and approximately 18% of patients develop grade 3 neuropathy. Other quoted side effects in literature include cold related transient paraesthesia, allergic reactions, coronary artery spasm, neutopaenia, thyrombocytopaenia, diarrhoea and mucositis. On the other hand, FOLFIRI shares most of the side effect profiles apart from the neuropathy caused by Oxaliplatin. The Irinotecan part of FOLFIRI can cause severe diarrhoea and approximately 13% of patients develop grade 3-4 diarrhoea, in addition it may lead to asthenia and is associated with a cholinergic syndrome characterized by rhinitis, increased salivation, lacrimation, diaphoresis and flushing. [9-10]

A significant number in our sample did not complete their treatment 41% (N=43). 10 patients were deceased; all of those patients had evidence of disease progression. 15 other patients had disease progression with expansion of the metastatic deposits, this heralded the chemotherapy futile and patients were sent for palliative care. 8 patients experienced significant complications like deep venous thrombosis, pulmonary embolism and arterial embolism; however of those only two patients stopped chemotherapy. In the other 16 patients the reason for discontinuation of chemotherapy was not clear from the data available. Other plausible explanations for why patients may

not have completed their treatment include the increasing financial or mobility barriers to care, preference changes, presence of comorbid conditions or mainly the debilitating chemotherapy-induced side effects.[7]

It is imperative to emphasize that systemic chemotherapy in metastatic colorectal cancer is usually not curative. However it is important to note that because the completion of chemotherapy is associated with increased survival, it is essential to complete the chemotherapy cycles once initiated. Nonetheless, in countries that do not have sufficient funds to administer chemotherapy, it is appropriate to forego chemotherapy and focus on palliative care. It must also be noted that, where available, a multidisciplinary approach and resection of oligometastatic disease and systemic treatment may cure some patients with metastatic colorectal cancer.[7]

Clinicians and patients should consider all this information aided by evidence based data and the extensive national statistics highlighted in this study to base treatment decisions. Afterall by balancing potential benefits, the probability of treatment completion, toxicity of treatment, quality of life and overall patient preferences an informed treatment approach can be undertaken.

Conclusion

As referring physicians, we have to appreciate that a large proportion of referred patients for adjuvant or palliative chemotherapy do not proceed smoothly with their treatment. Many of those patients are middle aged fully functional individuals. Although chemotherapy increases survival in metastatic colorectal cancer, many patients do not complete the whole chemotherapy regimen due to debilitating side effects or disease progression. Both chemotherapies are found to be comparatively equivalent, however FOLFOX is usually preferred due to a more tolerable side effect profile, FOLFIRI is usually reserved as second line treatment, as a test for efficacy. After all, the physician must be confident to draw the line at the appropriate time and rather focus on palliative care.

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