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Neutropaenia as a prognostic factor in metastatic colorectal cancer patients undergoing chemotherapy with first-line FOLFOX

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ABSTRACT

We retrospectively analysed 153 patients with metastatic colorectal cancer who received FOLFOX with or without bevacizumab as first-line chemotherapy. Several background characteristics and chemotherapy features (grade of neutropaenia, use of bevacizumab or irinotecan, re-introduction of FOLFOX, and tumour progression) as time-varying covariates were analysed as potential prognostic factors. Of the 153 patients, mild neutropaenia (grade 1–2) occurred in 60 patients (39%) and severe neutropaenia (grade 3–4) occurred in 46 patients (30%). The other 47 patients (31%) did not experience neutropaenia. According to a multivariate Cox model with time-varying covariates, hazard ratios (HRs) of death were 0.55 (95% confidence interval (CI), 0.31–0.98; $P = 0.044$) for patients with mild neutropaenia and 0.35 (95% CI, 0.18–0.66; $P = 0.002$) for those with severe neutropaenia. Both mild and severe neutropaenia during chemotherapy are associated with improved survival in patients with MCRC. Prospective trials are required to assess whether dosing adjustments based on neutropaenia may improve chemotherapy efficacy.

1. Introduction

Neutropaenia due to cytotoxic chemotherapy is a common type of adverse event. Severe neutropaenia predisposes to lethal infection, but it is rarely fatal because of recent improvements in supportive therapy. Neutropaenia during cytotoxic chemotherapy for several types of cancer has also been reported to be associated favourably with survival.[1–6]

A possible explanation for neutropaenia's favourable impact on survival is that it is a surrogate marker for a sufficient anti-tumour dose of cytotoxic chemotherapy. In general, recommended doses of cytotoxic agents are determined in dose-finding studies that determine toxicity profiles. Sample sizes in this study phase are not large enough to examine individual differences in drug metabolism; therefore, toxicity profiles are likely to be highly variable.[7] Because of the nature of dose-finding studies, a standard dose may be insufficient for those patients with faster drug elimination times.[7] Supporting this hypothesis are several early reports on the toxicity-response relationships of cytotoxic chemotherapy used for breast cancer,[1] testicular cancer,[2] ovarian cancer[3] and lymphoma.[4]

Recently Di Maio and colleagues using pooled data from randomised controlled trials reported that neutropaenia

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(grades 1–2 or grades 3–4) during chemotherapy was associated with prolonged survival in patients with advanced non-small-cell lung cancer compared to patients who did not experience neutropaenia.[5] A similar result was also reported in gastric cancer.[6] However, the effect of chemotherapy-induced neutropaenia on clinical outcome has not yet been reported in metastatic colorectal cancer (MCRC).

In this report, we describe a retrospective analysis of patients with MCRC who were treated with the first-line chemotherapy FOLFOX, in order to evaluate any possible association between neutropaenia occurring during chemotherapy and survival.

2. Patients and methods

2.1. Patients

This was a retrospective cohort study of MCRC patients who received FOLFOX as first-line chemotherapy. Principal inclusion criteria were as follows: the presence of histologically proven, inoperable colorectal cancer; age less than 80 years; Eastern Cooperative Oncology Group performance status (PS) of 0 or 1; sufficient bone marrow function (neutrophil count $\geqslant 2.0\times10^9$/L, leucocyte count $\geqslant 4.0\times10^9$/L, platelet count $\geqslant 100\times10^9$/L, haemoglobin $\geqslant 9.0$ g/dL); normal liver and renal function; and no history of prior chemotherapy for advanced disease.

Between April 2005 and August 2007, 264 patients with MCRC were treated and 153 patients were identified who met the inclusion criteria. Written informed consent was obtained from all patients.

2.2. Treatment delivery

Patients received either FOLFOX-4 (consisting of a 2-h infusion of leucovorin isomers [l-LV] at 100 mg/m^2 followed by a bolus of 5-FU at 400 mg/m^2 plus a 22-h infusion of 5-FU at 600 mg/m^2 for two consecutive days every 2 weeks, with oxaliplatin 85 mg/m^2 as a 2-h infusion on day 1); or modified FOLFOX-6 (consisting of a 2-h infusion of l-LV at 200 mg/m^2 followed by a 5-FU 46-h infusion of 2400 mg/m^2 every 2 weeks, with oxaliplatin at 85 mg/m^2 as a 2-h infusion on day 1). Patients with or without bevacizumab were included. Chemotherapy was delayed until recovery for a neutrophil count $< 1.0\times10^9$/L, platelet count $< 75\times10^9$/L, or any significant persisting non-haematologic toxicity. The 5-FU bolus and infusional doses were reduced by 20% if the National Cancer Institute criteria for grade 3 common side-effects of diarrhoea, anorexia or stomatitis occurred. In case of grade 4 neutropaenia, febrile neutropaenia or grade 3–4 thrombocytopaenia, the doses for oxaliplatin and 5-FU were reduced by 20%, or the 5-FU bolus was omitted from the regimen. In cases of persistent (14-d) painful paraesthesia or functional impairment, oxaliplatin was omitted from the regimen, or chemotherapy was discontinued until recovery. Other dose adjustments were made on an individual basis. Treatment was discontinued if the tumour progressed, severe toxicity occurred or at the patient's request.

The actual dose intensity was defined as the total dose of drug delivered per unit of body surface area per time unit (mg/m^2/week). The relative dose intensity of each drug was calculated as the ratio between actual dose intensity and the scheduled dose intensity.

2.3. Evaluation of neutropaenia and supportive therapy

A complete blood cell count was performed biweekly prior to each chemotherapy cycle. Patients with treatment delay due to toxicity were followed up with weekly or more frequent blood counts. The most severe grade of neutropaenia was based on the lowest recorded neutrophil count for a given patient between the first day of FOLFOX administration and 2 weeks after the last FOLFOX cycle was administered, and was graded according to the National Cancer Institute Common Toxicity Criteria version 3.0. To evaluate neutropaenia during chemotherapy, patients were divided into three categories: neutropaenia absent (grade 0), mild (grades 1–2), and severe (grades 3–4).

The indication for using granulocyte-colony-stimulating factor (G-CSF) was not defined, but G-CSF was generally used in grade 4 neutropaenia or in febrile neutropaenia, and no use as prophylaxis was allowed.

2.4. Statistical methods

The primary end-point of this study was to evaluate the association between neutropaenia during FOLFOX treatment and overall survival, which was defined as the interval between the date of beginning FOLFOX treatment and the date of death or last follow-up.

To evaluate the impact of neutropaenia on overall survival, univariate and multivariate Cox proportional hazards modelling was applied. Therefore, a measure of association in this study was the hazard ratio (HR) along with the 95% confidence interval (95% CI). As some of the assessed characteristics varied over time, analysis was performed with or without time-varying covariates (TVCs).

Forward and backward stepwise methods were used for model building. Threshold P values for inclusion or exclusion in the model were defined as 0.10 and 0.20, respectively. Confounders considered in the uni- and multivariate analyses were age (less than 65 versus 65 or older), gender (male: 0 versus female: 1), ECOG performance status (PS) (0 versus 1), primary location of tumour (colon: 0 versus rectum: 1), disease status (recurrent: 0 versus advanced: 1), number of metastatic sites (1 versus $\geqslant$2), adjuvant chemotherapy (yes: 0 versus none: 1), serum level of alkaline phosphatase (ALP) (within normal range: 0 versus increased: 1), serum level of lactate dehydrogenase (LDH) (within normal range: 0 versus increased: 1), serum level of carcinoembryonic antigen (CEA) (within normal range: 0 versus increased: 1) and leucocyte count ($\leqslant 8.0\times10^9$/L: 0 versus $>8.0\times10^9$/L: 1).

TVCs were defined as highest grade of neutropaenia during FOLFOX treatment (1: absent versus 2: mild versus 3: severe), use of bevacizumab (yes: 0 versus none: 1), use of salvage therapy by irinotecan (yes: 0 versus none: 1), re-introduction of oxaliplatin (yes: 0 versus none: 1) and tumour progression (yes: 0 versus none: 1). Since some patients received bevacizumab as an add-on to FOLFOX after Japanese regula-

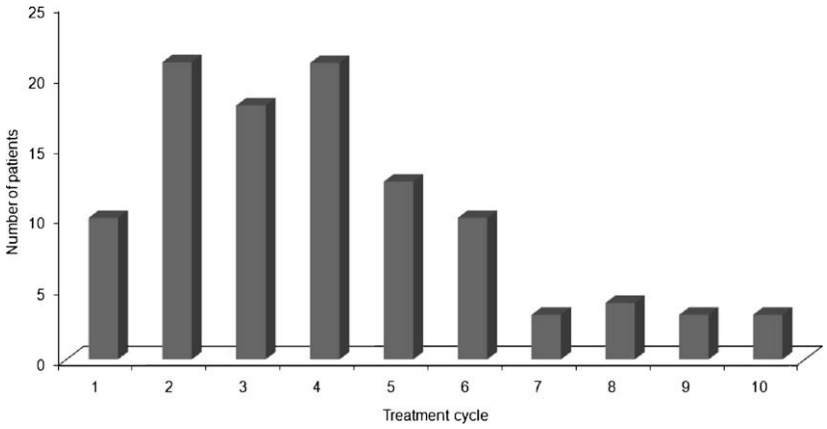

Fig. 1 – *The timing of occurrence of neutropaenia with highest grade.* In 106 patients experiencing neutropaenia, the highest grade was seen during the first cycle in 10 patients, during the second cycle in 21, during the third cycle in 18 and during the fourth cycle in 21 patients, indicating that 66% of patients with neutropaenia experienced their highest grade within four cycles.

tory approval, and some patients received bevacizumab as salvage chemotherapy with irinotecan and/or 5-FU, use of bevacizumab was considered a TVC.

Distribution of subject characteristics was assessed by the chi-square test or by the Fisher exact test, as appropriate. Statistical analyses were performed using STATA ver. 10 (StataCorp

Table 1 – Patient characteristics according to most severe neutropaenia.

Characteristics		All (n = 153)	Grade 0 (n = 47)	Grades 1–2 (n = 60)	Grades 3–4 (n = 46)
Median age		62	64	61	62
Gender	Male	94	33	37	24
	Female	59	14	23	22
ECOG PS	0	84	27	29	28
	1	69	20	31	18
Origin	Colon	96	35	28	33
	Rectum	57	12	32	13
Disease status	Advanced	83	23	36	24
	Recurrent	70	24	24	22
Metastatic site	1	79	26	29	24
	2⩽	74	21	31	22
Adjuvant chemotherapy	Yes	45	12	21	12
	No	108	35	39	34
ALP	WNL	94	26	38	30
	Increased	59	21	22	16
LDH	WNL	85	21	37	27
	Increased	68	26	23	19
CEA	WNL	36	11	13	12
	Increased	117	36	47	34
Leucocyte count	$\leqslant 8.0 \times 10^9$/L	125	35	51	39
	>8.0 × 109/L	28	12	9	7
Bevacizumab use	Yes	46	13	16	17
	No	107	34	44	29
Oxaliplatin re-introduction	Yes	26	10	5	11
	No	127	37	55	35
Irinotecan use	Yes	106	33	37	36
	No	47	14	23	10
Median cycles		10	8	11	10
Dose intensity	Oxaliplatin	0.88	0.92	0.89	0.86
	Leucovorine	0.91	0.93	0.90	0.89
	5-FU bolus	0.84	0.90	0.88	0.77
	5-FU infusion	0.89	0.93	0.89	0.83
Death/censored		80/73	30/17	29/31	21/25

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ALP, alkaline phosphatase; CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase; WNL, within normal range; and 5-FU, 5-fluorouracil.

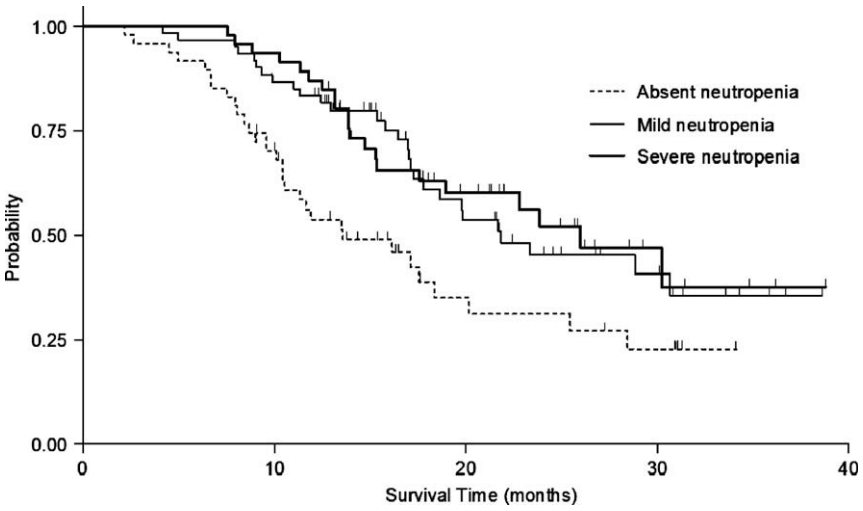

Fig. 2 – *Kaplan–Meier survival curves according to most severe neutropaenia that occurred*. Median overall survivals of absent group, mild group and severe group were 13.6 months, 21.7 months and 26 months, respectively.

LP, College Station, TX, USA). All tests were two-sided, and *P* values less than 0.05 were considered statistically significant.

3. Results

3.1. *Patient characteristics*

The median follow-up time at the time of this analysis was 26 months. Overall, mild neutropaenia (grades 1–2) occurred in 60 (39%) of 153 patients and severe neutropaenia (grades 3–4) occurred in 46 (30%). The other 47 patients (31%) did not experience neutropaenia during treatment with FOLFOX. In 106 patients experiencing neutropaenia, the highest grade was seen during the first cycle in 10 patients, during the second cycle in 21, during the third cycle in 18, during the fourth cycle in 21 and during the fifth cycle or thereafter in 36, indicating that 66% of patients with neutropaenia experienced their highest grade within four cycles (Fig. 1). On the other hand, 13 of 60 patients (21%) without neutropaenia within four cycles experienced late-onset neutropaenia (11 patients with mild neutropaenia and two patients with severe neutropaenia).

Patient characteristics categorised according to highest grade neutropaenia experienced are shown in Table 1. Only the site of primary tumour (rectum or colon) was significantly different. No other significant difference was seen between the three neutropaenia groups, including the use of bevacizumab, irinotecan or re-introduction of oxaliplatin.

The median number of treatment cycles was slight fewer in patients with absent neutropaenia (eight cycles, range 3–17) than with mild (11 cycles, range 2–17) or severe neutropaenia (10 cycles, range 4–20), although the relative dose intensity was not significantly different between each group (Table 1).

The median overall survival time of all patients was 20 months (95% CI, 17.1–26.0). Kaplan–Meier survival curves according to chemotherapy-induced neutropaenia are shown in Fig. 2. The median overall survival times in the absent group, mild group and severe group were 13.6 months (95% CI, 10.4–20.1), 21.7 months (95% CI, 17.1–not reached) and 26 months (95% CI, 15.3–not reached), respectively.

Grade 2 thrombocytopaenia was seen in 10 patients (1 patient without neutropaenia), and no patients developed the complication of grades 3–4 thrombocytopaenia. Regarding non-haematological toxicities, grade 2 neuropathy was seen in 68 patients (44%) and five patients (3%) developed grade 3 neuropathy. The incidence of other non-haematological grade 3–4s toxicities was low (diarrhoea in three patients, anorexia in four patients, fatigue in four patients and vomiting in two patients).

3.2. *Survival analyses without TVCs*

Table 2 shows the results of univariate and multivariate analyses of baseline and clinical characteristics as prognostic factors, including neutropaenia. Neutropaenia and four other factors were identified as statistically significant in univariate analyses, and four factors including neutropaenia remained significant in multivariate analyses. The HR for mild neutropaenia in comparison to absent neutropaenia was 0.38 (95% CI, 0.22–0.66; $P = 0.001$), and the HR for severe neutropaenia in comparison to absent neutropaenia was 0.35 (95% CI, 0.19–0.64; $P = 0.001$). Other significant factors associated with improved prognosis were male gender, PS = 0 and normal ALP levels.

3.3. *Survival analyses with TVCs*

Table 2 also shows the result of multivariate regression analyses with TVCs included. Gender, PS and ALP levels remained highly significant among the baseline characteristics. Among five TVCs, neutropaenia, use of bevacizumab and tumour progression were highly statistically significant prognostic factors. The HR for mild neutropaenia in comparison to absent neutropaenia was 0.55 (95% CI, 0.31–0.98; $P = 0.044$), and the HR for severe neutropaenia in comparison to absent neutropaenia was 0.35 (95% CI, 0.18–0.66; $P = 0.002$). In contrast to the use of bevacizumab, salvage chemotherapy with irinotec-

Table 2 – Univariate and multivariate analyses with or without TVCs.

Baseline and clinical features	Univariate analysis without TVC			Multivariate analysis without TVC			Multivariate analysis with TVC		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Neutropaenia: grade 1–2 ($n = 60$) versus grade 0 ($n = 47$)	0.52	0.31–0.87	0.01	0.38	0.22–0.66	0.001	0.55	0.31–0.98	0.044
Grade 3–4 ($n = 46$) versus grade 0 ($n = 47$)	0.48	0.27–0.84	0.01	0.35	0.19–0.64	0.001	0.35	0.18–0.66	0.002
Bevacizumab use: yes ($n = 46$) versus no ($n = 107$)	–	–	–	–	–	–	0.45	0.22–0.93	0.031
Irinotecan use: yes ($n = 106$) versus no ($n = 47$)	–	–	–	–	–	–	0.74	0.42–1.2	0.28
Oxaliplatin re-introduction: yes ($n = 26$) versus no ($n = 127$)	–	–	–	–	–	–	0.73	0.31–1.6	0.45
Tumour progression: yes ($n = 125$) versus no ($n = 28$)	–	–	–	–	–	–	35.50	8.2–153	<0.001
Age: $\geqslant 65$ ($n = 55$) versus <65 ($n = 98$)	1.15	0.73–1.83	0.53	–*	–*	–*	–*	–*	–*
Gender: female ($n = 59$) versus male ($n = 94$)	1.50	0.95–2.35	0.08	2.10	1.2–3.4	0.003	2.06	1.3–3.4	0.005
ECOG PS: 1 ($n = 69$) versus 0 ($n = 84$)	2.62	1.66–4.14	<0.001	3.85	2.3–6.3	<0.001	3.30	1.9–5.6	<0.001
Primary: rectum ($n = 57$) versus colon ($n = 96$)	0.63	0.39–1.01	0.06	–*	–*	–*	0.68	0.41–1.1	0.14
Status: advanced ($n = 83$) versus recurrent ($n = 70$)	1.26	0.81–1.96	0.30	–*	–*	–*	–*	–*	–*
No. of metastatic sites: >1 ($n = 74$) versus 1 ($n = 79$)	1.68	1.07–2.6	0.02	–*	–*	–*	–*	–*	–*
Adjuvant: yes ($n = 45$) versus no ($n = 108$)	0.85	0.52–1.4	0.53	–*	–*	–*	0.64	0.39–1.1	0.10
ALP: increased ($n = 59$) versus WNL ($n = 94$)	2.06	1.3–3.2	0.002	2.81	1.7–4.5	<0.001	2.04	1.2–3.3	0.005
LDH: increased ($n = 68$) versus WNL ($n = 85$)	1.94	1.24–3.03	0.004	–*	–*	–*	–*	–*	–*
CEA: increased ($n = 117$) versus WNL ($n = 36$)	1.47	0.83–2.58	0.18	–*	–*	–*	–*	–*	–*
Leucocyte: $>8.0 \times 10^9$/L ($n = 28$) versus $\leqslant 8.0 \times 10^9$/L ($n = 125$)	1.34	0.77–2.33	0.29	–*	–*	–*	–*	–*	–*

Abbreviations: TVC, time-varying covariates; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen; and WNL, within normal range.
* Indicates variable excluded from the model by the stepwise method.

an or re-introduction of oxaliplatin was not associated with improved prognosis.

If the analysis of neutropaenia was limited to four cycles of FOLFOX, mild or severe neutropaenia remained a significant prognostic factor according to survival analysis with or without TVCs (data not shown). Moreover, in subgroup analyses, both mild and severe neutropaenia tended to be associated with improved prognosis in almost all subgroups (Fig. 3). Additionally, in almost all subgroups, both severe and mild neutropaenia were favourable prognostic factors to almost the same degree.

4. Discussion

In this study, we found significantly improved survival in patients who experienced neutropaenia during FOLFOX treatment as first-line chemotherapy for MCRC. The frequencies of neutropaenia in this study were comparable to past clinical study reports where FOLFOX regimens were used.[8–10] Our results indicate that both mild and severe neutropaenia during chemotherapy have a significant impact on the risk of death (HR = 0.55 in mild neutropaenia and HR = 0.35 in severe neutropaenia) after adjustment for baseline prognostic factors and other TVCs. To the best of our knowledge, this is the first evidence of this phenomenon in MCRC. From our observation, we speculate that neutropaenia might be a surrogate marker of the adequate dose of chemotherapeutic agents to cause bone marrow suppression as well as antitumour effect. In other words, lack of neutropaenia suggests an absent or weak biological effect of chemotherapy possibly due to under dosing for each patient. The cause of this interpatient variation is unclear, although some gene polymorphisms which relate to drug metabolism or elimination might be one explanation.

Since neutropaenia does not exist prior to the initiation of chemotherapy, a false association between neutropaenia and patient outcome might have been observed because of a higher incidence of neutropaenia with increasing cycles of chemotherapy in patients with better prognosis (length-bias sampling). Therefore, to answer our *a priori* hypothesis, Cox proportional hazards modelling was applied to remove confounding factors and neutropaenia as TVCs, and is one of the strengths of this study. Furthermore, we further evaluated the impact of neutropaenia during the first four cycles of FOLFOX on survival and found that neutropaenia within the first four cycles also showed improved survival, similar to the occurrence of neutropaenia in all cycles.

In this study, 66% of patients with neutropaenia (70 of 106 patients) experienced their highest grade within four cycles, and those without neutropaenia occurring in the first four cycles rarely experienced severe late-onset neutropaenia (2 of 60 patients, 3%; 95% CI: 0.4–11%). This finding provides some insight into dose intensity/increments for FOLFOX treatment of MCRC, to be evaluated in the future. Taking into consideration the better prognosis seen in patients developing neutropaenia, those who do not experience neutropaenia within the first four cycles should receive more intensive treatment. Therefore, neutropaenia in earlier cycles can be used as a

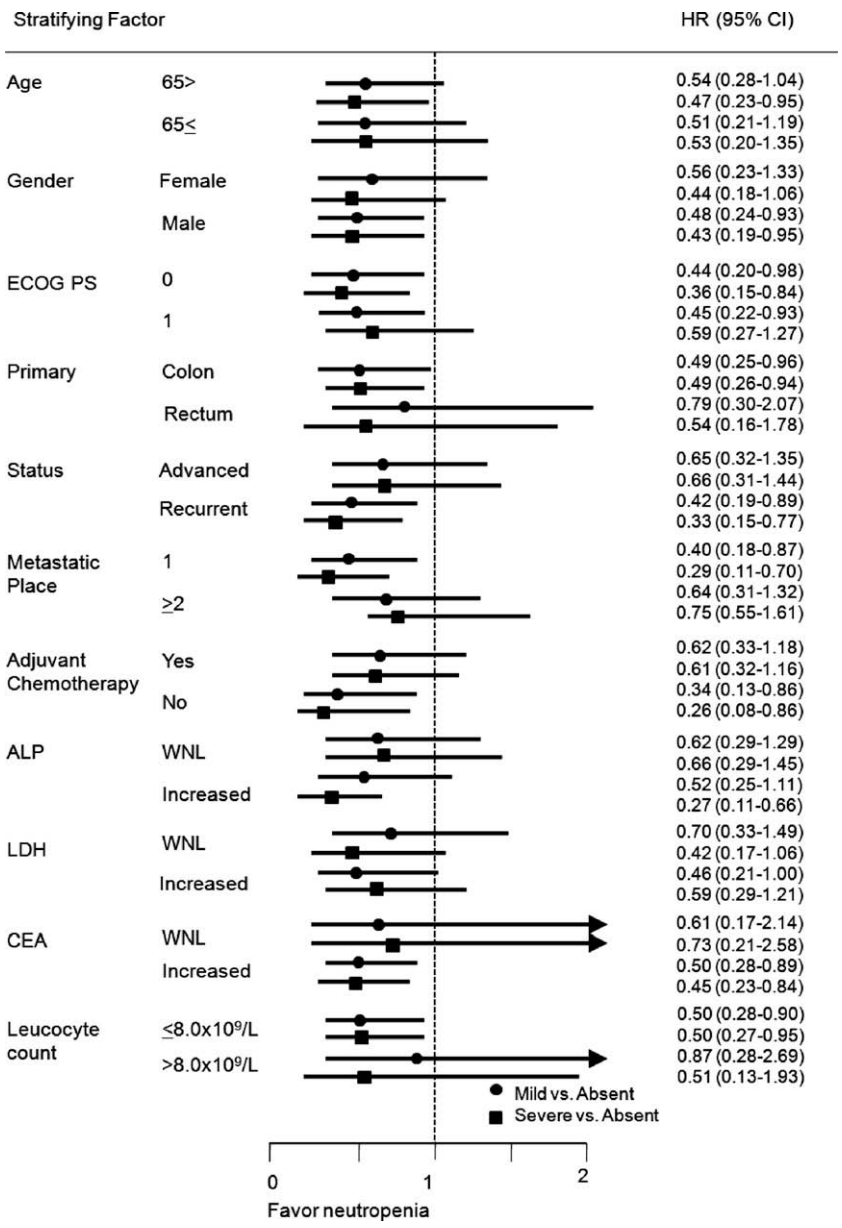

Fig. 3 – *Hazard ratios (HRs) for death and 95% CIs*. In subgroup analyses, both mild and severe neutropaenia tended to be associated with improved prognosis in almost all subgroups.

surrogate marker for adequate-intensity FOLFOX treatment. Therefore, future evaluation of this procedure is strongly warranted.

In survival analysis including TVCs, tumour progression is strongly associated with poor survival; however, this is self-evident since patients are at a much greater risk of death after tumour progression. Among the three treatment-related TVCs (bevacizumab, irinotecan and oxaliplatin re-introduction), only the use of bevacizumab was associated with improved survival. Although randomised control trial is essential to evaluate the benefit of a new drug on survival, the importance of bevacizumab for the treatment of MCRC was also suggested in this study.

There are several methodological issues. This study was a retrospective cohort design evaluating the association between neutropaenia as an exposure of interest and overall survival. Unlike a typical exposure of interest such as treatment assignment, neutropaenia is less likely to be influenced by the investigator's intention. Therefore, our finding should be valid. Taking into consideration the analyses of the time-varying nature of exposure as well as other covariates (bevacizumab, etc.), along with a sensitivity analysis of neutropaenia occurring within four cycles also contributes to the strengths of our findings. A moderate sample size may be a study limitation that requires duplicating this work in another independent cohort.

In conclusion, neutropaenia occurring during FOLFOX treatment as a first-line treatment in MCRC patients is strongly associated with better prognosis. This might indicate that neutropaenia is a surrogate marker for adequate anti-tumour doses of chemotherapeutic agents. An additional well-defined prospective trial is warranted.

Conflict of interest statement

None declared.

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