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Review

Efficacy and tolerability of chemotherapy in elderly patients with advanced oesophago-gastric cancer: A pooled analysis of three clinical trials

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ABSTRACT

The aim of this study was to determine the benefits of chemotherapy for oesophago-gastric cancer (OGC) in patients 70 years and above (⩾70) in comparison to younger patients. 1080 patients were enrolled into three randomised controlled trials assessing fluorouracil-based combination chemotherapy. Patients received either a platinum-containing regimen (ECF, MCF), PVI 5-FU (protracted venous infusion of 5-fluorouracil) ± mitomycin C (MMC), or FAMTX. Of the 1080 patients randomised, 257 (23.8%) were aged ⩾70 years. There were no significant differences in the incidence of grades 3/4 toxicity between the two cohorts. Objective and symptomatic response rates, failure-free and overall survival were not significantly different. In a multivariate analysis, independent prognostic factors for survival were performance status and locally advanced disease, not age. Patients ⩾70 years with OGC obtained similar benefits from palliative chemotherapy with respect to symptomatic response, tumour regression and survival, without increased toxicities.

1. Introduction

In 1999, cancer was second only to cardiovascular diseases as a leading cause of death.[1] Twelve percent of population from USA was aged 65 years or more in 2000.[2] This is expected to rise rapidly reaching 20% of the population by 2050.[2] Similarly, in the European Union the proportion of the population aged over 65 years is expected to increase from 15% in 1995 to 17.1% by 2010.[3] People aged 65 years and older account for 61% of all new cancer cases and 70% of all cancer deaths.[4] Cancers of the oesophagus and stomach together are the fourth most frequent malignant diseases and causes of cancer death with the majority of cases occurring in the seventh and eighth decade.

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The majority of patients with oesophago-gastric cancer have locally inoperable or metastatic disease at presentation. Systemic chemotherapy has established quality of life and survival advantages compared to supportive care alone.[5–7] Cisplatin and 5-fluorouracil (5-FU)-based chemotherapy regimens have been used most frequently in previously untreated patients. However, there is uncertainty to the extent of systemic palliative chemotherapy that should be offered to elderly patients. This is a consequence of the under-representation of elderly patients in clinical trials.[8,9] In advanced colorectal cancer, two analyses have examined the outcomes from palliative chemotherapy in patients aged 70 years or older (⩾70 years).[10,11] Both concluded that elderly patients with good performance status benefit from chemotherapy with 5-FU at least to the same extent as younger patients. Furthermore, Chau and colleagues demonstrated that patients ⩾70 years with colorectal cancer achieved the same benefit as younger patients from second-line chemotherapy with irinotecan, without experiencing more toxicity.[12]

A few studies have investigated prognostic factors in locally advanced and metastatic oesophago-gastric cancer.[13–16] None have identified age as an independent prognostic factor. However, the proportion of patients aged ⩾70 years was not reported in any of these analyses.

To gain a better understanding of the potential benefit of systemic chemotherapy in elderly patients, we have undertaken a retrospective analysis using original data from 3 large multi-centre randomised trials. A total of 257 patients aged ⩾70 years were identified. To our knowledge this is the first such analysis conducted.

2. Patients and methods

2.1. Patients

Between 1992 and 2001, 1080 eligible patients were randomised in three multicentre prospective randomised controlled trials conducted in the United Kingdom evaluating chemotherapy in the management of locally advanced or metastatic cancer of the oesophagus, oesophago-gastric junction (OGJ) and stomach. The first study included 256 patients that were randomised to either the ECF regimen [epirubicin (50 mg/m^2 IV) and cisplatin (60 mg/m^2 IV) 3-weekly with protracted venous infused 5-fluorouracil (PVI 5-FU) (200 mg/m^2/day)] or the FAMTX regimen [methotrexate (1500 mg/m^2 IV) and 5-FU (1500 mg/m^2 IV) on day 1 followed by doxorubicin (30 mg/m^2 IV) on day 15 repeated every 4 weeks]. The second study randomised 574 patients to either the ECF regimen or the MCF regimen [mitomycin C (MMC) (7 mg/m^2 IV once every 6 weeks), cisplatin (60 mg/m^2 IV 3-weekly) and PVI 5-FU (300 mg/m^2/day)]. The third study randomised 250 patients to PVI 5-FU (300 mg/m^2/day) alone or in combination with MMC (7 mg/m^2 IV once every 6 weeks). A maximum treatment period of 24 weeks was planned in all three studies.

The three protocols had similar eligibility criteria. Patients were required to have histologically confirmed inoperable adenocarcinoma, squamous cell carcinoma or undifferentiated carcinoma of the oesophagus, OGJ or stomach; adequate haematological, renal and hepatic function, and Eastern Co-operative Group (ECOG) performance status (PS) 0–2. The differences in eligibility criteria were: (i) the first study excluded patients with squamous cell carcinoma; and (ii) the third protocol included patients inoperable due to co-morbidities.

Prior to randomisation, written informed consent was obtained from all patients. All three studies were approved by the Scientific and Research Ethics committees of the participating Institutions. Results from all three studies have been published.

2.2. Statistical methods

In all analyses, patients aged less than 70 years were compared to those aged ⩾70 years. Analyses were conducted based on chemotherapy regimen: platinum-containing (ECF and MCF), PVI 5-FU ± MMC, and FAMTX. Objective and symptom response rates were compared using the chi-squared test and Fisher's exact test where appropriate. Toxicity was graded 0–4 using the common toxicity criteria (CTC) and a comparison between groups for grade 3–4 toxicity was performed using the chi-squared test, all toxicity grades were compared using the chi-squared test for trend.

Overall survival (OS) was calculated from the date of randomisation until death from any cause or censored at last follow-up using the Kaplan–Meier method. Comparison of survival curves was performed using the log rank test. Survival analyses were performed on an intention to treat basis. Univariate assessment of the prognostic effect of age less than 70 years compared to ⩾70 years was performed. Multivariate analysis controlling for chemotherapy regimen received was performed using stepwise Cox proportional hazards regression modeling. Factors included in these analyses included performance status, extent of disease and age group. A two-sided P-value of <0.05 was considered statistically significant.

3. Results

3.1. Patient demographics

Of the 1080 patients randomised between 1992 and 2001, 257 (23.8%) were aged ⩾70 years. 160 patients were in the age group 70–74 years (14.8% of the study population), 78 in the age group 75–79 years (7.2%) and 19 in the group ⩾80 years (1.8%). The age distribution of all patients is shown in Fig. 1.

The patient characteristics within the different chemotherapy regimens and age categories (<70 or ⩾70 years) are shown in Table 1. A total of 75.7% of young patients and 61.9% of patients ⩾70 years had metastatic disease. This difference was significant ($P < 0.001$). There were no differences in other patient or tumour characteristics. In particular, there appeared to be no differences in the distribution of ECOG performance status.

3.2. Toxicity

The percentage of patients receiving chemotherapy and experiencing overall toxicity (CTC grades 1–4) and severe toxicity (CTC grades 3 and 4) is listed in Table 2. In addition, the incidence of severe toxicity is illustrated in Fig. 2. Haematological

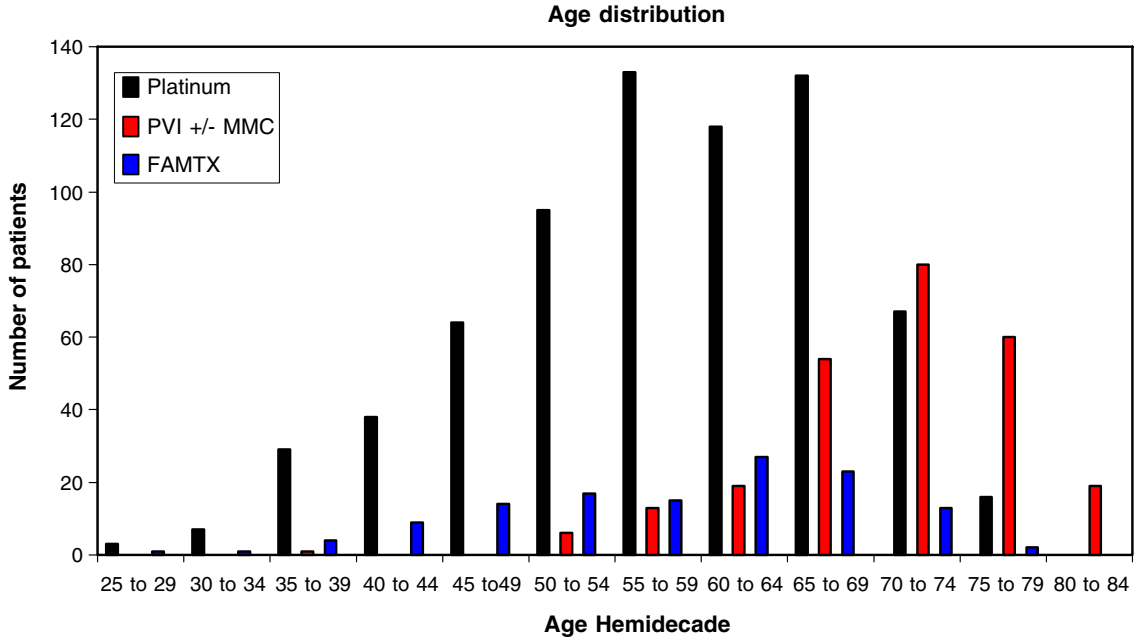

Fig. 1 – Age distribution of patients included in the analysis. Platinum-cisplatin + protracted venous infusion of 5-fluorouracil combined with either epirubicin or mitomycin C.

Table 1 – Patient characteristics stratified according to chemotherapy regimen and age

	Platinum-containing			PVI 5-FU ± MMC			FAMTX		
	<70 No. (%)	⩾0 No. (%)	*P*	<70 No. (%)	⩾70 No. (%)	*P*	<70 No. (%)	⩾70 No. (%)	*P*
No.	619	83		93	159		111	15	
Male	478 (77)	66 (80)		74 (80)	118 (74)		93 (84)	13 (87)	
PS									
0	125 (21)	6 (8)		10 (11)	10 (6)		18 (16)	0	
1	362 (59)	57 (71)		48 (53)	95 (61)		65 (59)	12 (80)	
2	121 (20)	17 (21)		32 (35)	49 (32)		24 (22)	3 (20)	
3	1 (0.2)	0		1 (1)	1 (1)		3 (3)		
Site of 1°									
Oesophageal	193 (31)	22 (27)	0.763	15 (16)	43 (26)	0.162	21 (19)	(20)	NS
OGJ	135 (22)	19 (23)		24 (26)	40 (25)		24 (22)	6 (40)	
Gastric	280 (45)	40 (48)		54 (58)	78 (49)		66 (60)	6 (40)	
Not known	11 (2)	2 (2)		0	0		0	0	
Histology									
Adenoca.	532 (91)	70 (84)		84 (94)	142 (92)		108 (97)	14 (93)	
Squamous	36 (6)	4 (5)		3 (3)	7 (4)		0	0	
Adenosq.	4 (1)	0		0	1 (1)		0	0	
Undiff.	5 (1)	1 (1)		1 (1)	1 (1)		3 (3)	1 (7)	
Not known	35 (1)	8 (10)		4 (1)	5 (2)		0	0	
Metastatic	463 (76)	44 (54)	<0.001	67 (72)	101 (64)	0.166	93 (84)	14 (93)	0.465

indices were missing for 14% of patients ⩾70 years and only 7% of patients <70 years. Non-haematological toxicity data was available for all patients. There were no statistically significant differences in overall or severe toxicity when patients aged <70 years were compared with those aged ⩾70 years.

Premature cessation of treatment was examined for patients treated with cisplatin-containing chemotherapy. In addition, dose-intensity was analysed for 5-FU across all treatment regimens. Cisplatin-containing chemotherapy was stopped prematurely in 41 of 83 (49%) patients ⩾70 years compared to 229 of 619 (37%) patients than those <70 years ($P = 0.06$). In patients ⩾70 years a dose intensity of 79.4% of the planned total dose was achieved compared to 87.3% for younger patients ($P < 0.0001$).

Table 2a – Common toxicity criteria grades 1–4 toxicities

	Platinum-containing			PVI 5-FU ± MMC			FAMTX		
	<70	⩾70	P	<70	⩾70	P	<70	⩾70	P
Non-haematological (%)									
Diarrhoea	42	50	0.09	37	40	0.636	43	25	0.896
Stomatitis	55	67	0.07	60	54	0.823	62	42	0.462
Nausea and vomiting	80	78	0.06	67	61	0.106	77	75	0.934
Alopecia	69	74	0.630	18	13	0.347	83	92	0.236
PPE	35	43	0.049	54	53	0.367	28	8	0.128
Infection	36	32	0.514	26	27	0.808	46	58	0.642
Haematological (%)									
Anaemia	79	85	0.697	76	67	0.133	81	93	0.309
Neutropaenia	68	78	0.148	16	15	0.981	67	71	0.563
Platelets	23	23	0.658	10	10	0.782	17	29	0.724

Table 2b – Common toxicity criteria grades 3/4 toxicities

	Platinum-containing			PVI 5-FU ± MMC			FAMTX		
	<70	⩾70	P	<70	⩾70	P	<70	⩾70	P
Non-haematological (%)									
Diarrhoea	5	10	0.173	6	4	0.545	5	17	0.289
Stomatitis	4	10	0.08	7	6	0.819	7	0	0.999
Nausea and vomiting	12	6	0.091	6	3	0.302	3	0	0.999
Alopecia	40	37	0.658	0	1	0.999	46	58	0.422
PPE	3	4	0.518	3	3	0.543	1	0	0.999
Infection	6	8	0.617	8	7	0.727	14	0	0.351
Haematological (%)									
Anaemia	10	5	0.229	15	8	0.10	11	21	0.458
Neutropaenia	30	36	0.304	4	5	0.745	54	64	0.488
Platelets	7	8	0.678	1	2	0.999	10	0	0.607

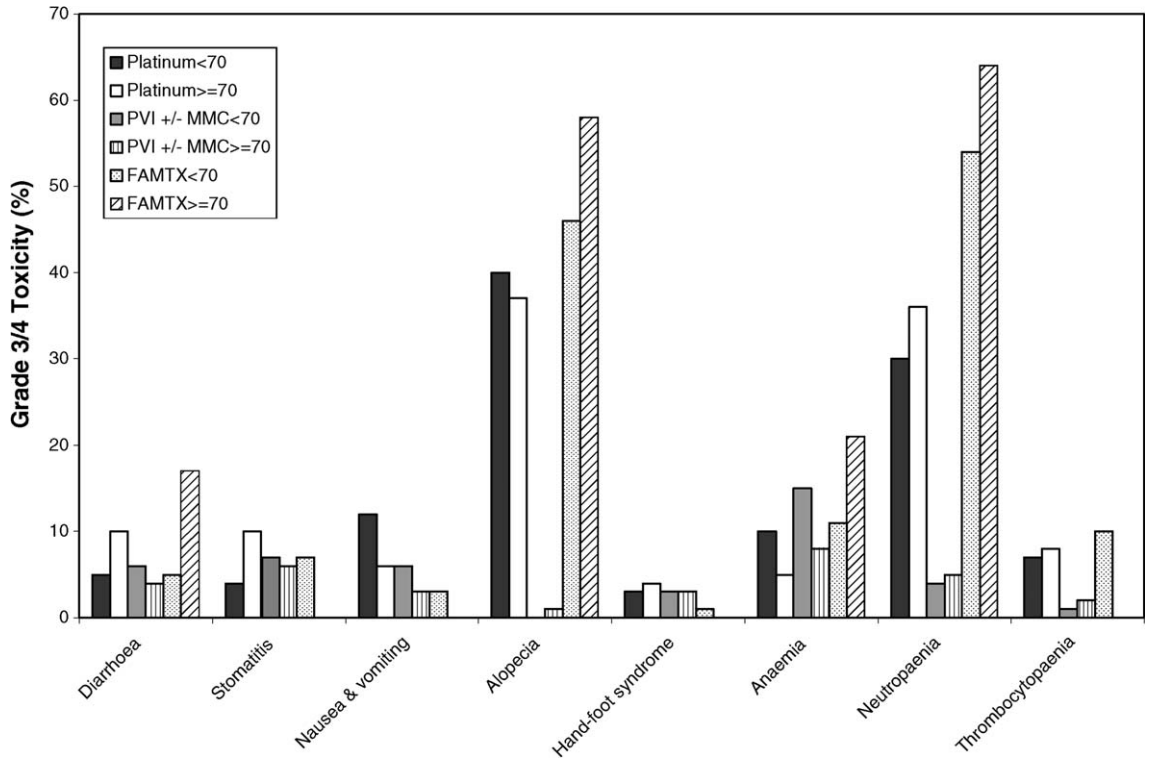

Fig. 2 – Grade 3/4 toxicity. Platinum-cisplatin + protracted venous infusion of 5-fluorouracil combined with either epirubicin or mitomycin C.

Table 3 – Objective response to chemotherapy

	Platinum-containing			PVI 5-FU ± MMC			FAMTx		
	<70	⩾70	P	<70	⩾70	P	<70	⩾70	P
Response (%)									
CR	9	10.1		3.3	0.7		2.8	0	
PR	34.8	32.9		14.4	16.5		18.4	6.7	
ORR	43.8	43.0	0.886	17.7	17.2	0.894	22.2	6.7	0.299
NR	30.0	26.6		26.7	34.9		32.1	40.0	
PD	17.3	13.9		37.8	34.9		23.9	20	
Died	8.9	16.5		17.8	13.2		22.9	33.3	
95% CI	39.9–47.9	31.9–54.7		10.5–27.3	11.1–23.1		13.4–28.8	0.2–32.0	
No. evaluable	597	79		90	152		109	15	

PVI 5-FU ± MMC, protracted venous infusion of 5-fluorouracil ± mitomycin C; FAMTX, 5-fluorouracil, doxorubicin + methotrexate; CR, complete response; PR, partial response; ORR, overall response rate; NR, no response; PD, progressive disease.

3.3. *Age-related response rates*

Objective tumour response rates to chemotherapy varied according to chemotherapy regimen but no age-related differences were observed (Table 3). The response rates for platinum-containing chemotherapy were 43.8% in patients <70 years compared to 43.0% in older patients ($P = 0.89$), for PVI 5-FU ± MMC were 17.7% vs. 17.2% ($P = 0.89$) and for FAMTX were 22.2% vs. 6.7% ($P = 0.30$).

Symptoms including weight loss, anorexia, and dysphagia occurred frequently at baseline with no significant differences in incidence at baseline between the two age cohorts. Lethargy occurred more frequently in the elderly (51% vs. 43%; $P = 0.017$), whereas nausea (32% vs. 23%; $P = 0.006$) and pain (56% vs. 44%; $P = 0.001$) were more frequent in patients <70 years. There were high rates of symptom response in patients <70 years and those ⩾70 years with no significant differences in response rates for any of the symptoms examined between the two age cohorts (Fig. 3).

3.4. *Survival*

Failure-free survival (FFS) and overall survival in patients ⩾70 years were not significantly different to that of younger patients (Table 4 and Figs. 4a, 4b). For patients treated with platinum-containing regimens 1-year FFS was 23.8% for the group <70 years and 26.5% for those ⩾70 years. 1-year overall survival was 35% in both age cohorts. Similarly, FFS and OS were similar for patients <70 years or ⩾70 years treated with either

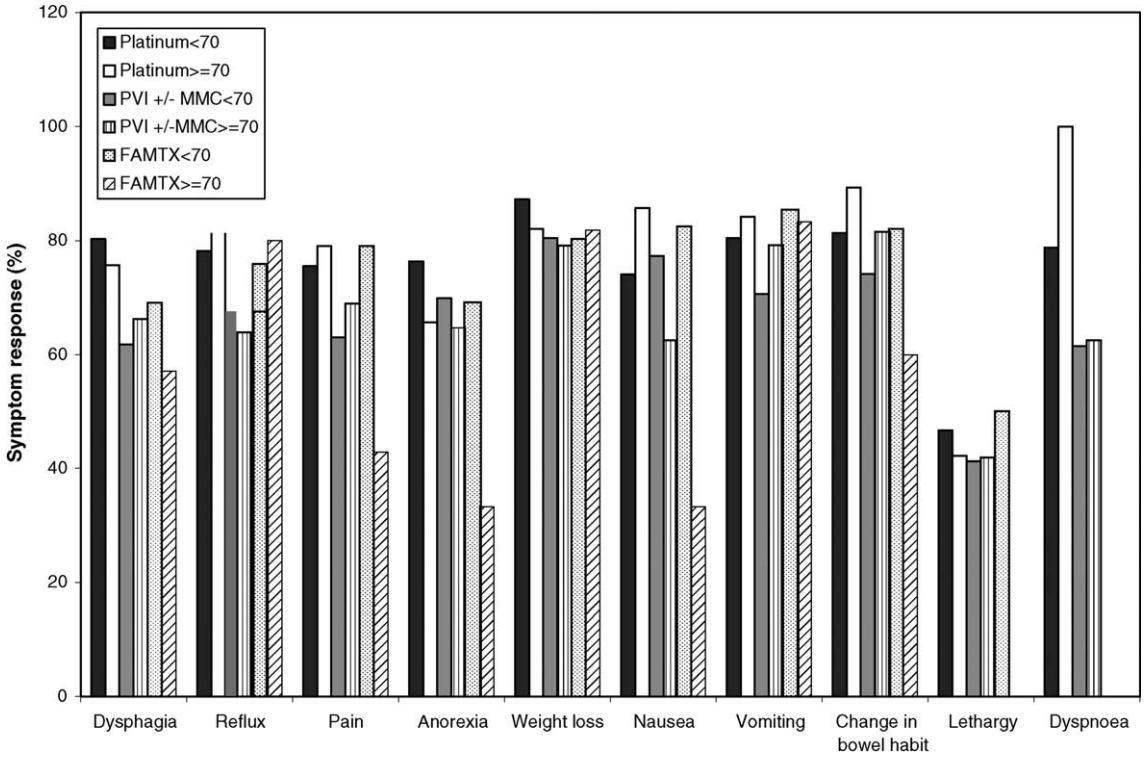

Fig. 3 – Symptom response. Platinum-cisplatin + protracted venous infusion of 5-fluorouracil combined with either epirubicin or mitomycin C.

Table 4 – Failure-free and overall survival

	Platinum-containing		PVI 5FU ± MMC		FAMTX	
	<70	⩾70	<70	⩾70	<70	⩾70
Overall survival						
One-year survival (%)	35.2	35.3	20	20.8	23.4	6.7
95% CI (%)	31–39	25–46	13–29	15–28	16–32	0–26
Median survival (months)	8.8	7.9	5.2	6.6	6.1	5.0
Failure-free survival						
One-year survival (%)	23.8	26.5	12.4	13.8	10.8	0
95% CI (%)	20–27	17–37	7–20	9–20	6–17	–
Median survival (months)	6.9	7.2	3.0	4.4	3.5	2.8

PVI 5-FU ± MMC, protracted venous infusion of 5-fluorouracil ± mitomycin C; FAMTX, 5-fluorouracil, doxorubicin + methotrexate.

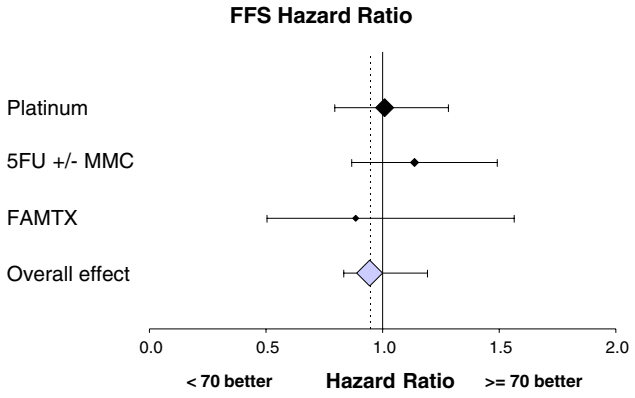

Fig. 4a – Failure-free survival hazard ratio. Platinum-cisplatin + protracted venous infusion of 5-fluorouracil combined with either epirubicin or mitomycin C.

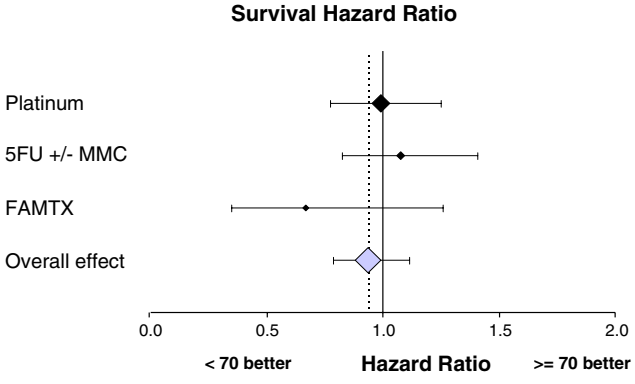

Fig. 4b – Survival hazard ratio. Platinum-cisplatin + protracted venous infusion of 5-fluorouracil combined with either epirubicin or mitomycin C.

PVI 5FU ± MMC or FAMTX. One-year overall survival for patients treated with these regimens was inferior to that for patients treated with platinum-containing chemotherapy (20% vs 35%). For platinum-containing regimens the hazard ratio for survival was 1.01 (95% CI 0.8–1.29), $P = 0.920$. For PVI 5FU ± MMC regimens the hazard ratio for survival was 0.93 (95% CI 0.71–1.21), $P = 0.566$ and for FAMTX the hazard ratio was 1.5 (95% CI 0.8–2.83), $P = 0.14$. The hazard ratios for failure-free survival were 0.99 (95% CI 0.78–1.26; $P = 1$), 0.88 (95% CI 0.67–1.15; $P = 0.351$) and 1.13 (95% CI 0.64–1.98; $P = 0.671$) for platinum-containing, PVI 5FU ± MMC and FAMTX chemotherapy regimens, respectively.

In a Cox regression analysis, age was not identified as a prognostic factor for either overall survival (HR 1.068, 95% CI 0.97–1.272; $P = 0.461$) or failure-free survival (HR 1.006, 95% CI 0.846–1.198; $P = 0.943$). Good performance status (0–1) and locally advanced disease were favourable prognostic factors for both overall and failure-free survival (Table 5).

4. Discussion

Using source data of 1080 patients with locally advanced or metastatic oesophago-gastric cancer, we identified 257 patients aged 70 years or older. Thus elderly patients represent 24% of the entire cohort. This does not reflect the proportion of patients with oesophago-gastric cancer that are aged ⩾70 years. Indeed, this figure for clinical trial participation of elderly patients with oesophago-gastric cancer is consistent with an analysis of clinical trial recruitment published by the National Cancer Institute (NCI).[8] The NCI found that patients 65 years or older with advanced oesophago-gastric cancer comprised just 39% of participants in 11 clinical trials, whereas the same cohort comprise 66% of patients.

In our analysis there were only minor differences in patient characteristics between patients ⩾70 years with those aged <70 years. A lower proportion of patients with metastatic disease were observed in the age group ⩾70 years. This may reflect physician bias, considering chemotherapy in older patients with metastatic disease less frequently. Indeed, elderly patients received platinum-containing chemotherapy for metastatic disease significantly less frequently than younger patients (43% vs. 60%; $P < 0.001$).

Efficacy of chemotherapy did not differ when patients ⩾70 years were compared to younger patients. The response rates varied with type of chemotherapy being 43% with platinum-containing chemotherapy compared to 17% with PVI 5-FU ± mitomycin C and 6% with FAMTX for patients ⩾70 years. There was no significant difference in response rate with each type of chemotherapy associated with age, although interpretation of these results is limited in the FAMTX group given the small number of elderly patients receiving this regimen. The difference in response rates between the three types of schedule are consistent with published data.[17–19] Similarly although there were some differences in symptoms at

Table 5 – Multivariate analyses for overall and failure-free survival

	Group	N	HR	Lower 95%	Upper 95%	P
Survival						
Age group	<70	810	1.068	0.897	1.272	0.461
	⩾70	250				
LAD	Locally advanced	284	0.636	0.548	0.738	<0.001
	Metastatic	776				
PS	0–1	808	0.668	0.576	0.775	<0.001
	2–3	252				
Failure-free survival						
Age group	<70	810	1.006	0.846	1.198	0.943
	⩾70	250				
LAD	Locally advanced	284	0.644	0.555	0.747	<0.001
	Metastatic	776				
PS	0–1	808	0.694	0.599	0.804	<0.001
	2–3	252				

baseline associated with age there was no significant difference in rates of symptom response.

Failure-free survival and overall survival were similar irrespective of age. Indeed, a multivariate analysis confirmed that age ⩾70 years as compared with <70 years was not a prognostic factor for survival. The multivariate analysis demonstrated that prognostic factors for survival were performance status and disease stage. In a previous analysis with pooled data on these 1080 patients, Chau and colleagues identified performance status, presence of liver and/or peritoneal metastases and serum alkaline phosphatase as significant prognostic factors.[13] One analysis has examined prognostic factors in a cohort of 350 patients with locally advanced or metastatic oesophageal cancer treated in six consecutive non-randomised studies with cisplatin-based chemotherapy.[15] Poor performance status, extensive disseminated disease and elevated lactate dehydrogenase level were associated with poor survival on multivariate analysis. The studies of both Chau and Polee found that survival varied according to the presence of 0, 1, 2 or 3 risk factors.

The absence of a negative influence of age on chemotherapy efficacy is similar to the situation found in colorectal cancer. An analysis using source data of 3825 metastatic colorectal cancer patients included in 22 European trials identified 629 (16.4%) patients aged ⩾70 years.[11] The response rate (21.1% vs. 23.9%; $P = 0.14$) and median overall survival (11.3 months vs. 10.8 months; $P = 0.31$) were similar in the two age cohorts. Furthermore, no trends in response rates, progression-free survival or overall survival were seen between patients of 70–74, 75–79, and ⩾80 years of age. A series from the Royal Marsden Hospital, that included 844 patients with advanced colorectal cancer of which 186 (22.0%) were aged ⩾70 years similarly found no significant difference in response rates (29% vs. 24%; $P = 0.19$) or failure-free survival (169 days vs. 164 days) between the two age cohorts.[10] However, overall survival was shorter in the patients aged ⩾70 years (350 days vs. 292 days; $P = 0.04$). This was related to a higher rate of non-cancer deaths in the older patients. Similarly, the response rate (11.1% vs. 9%; $P = 0.585$) and survival ($P = 0.74$) with second-line irinotecan in advanced colorectal cancer were no different in patients aged ⩾70 years and those aged <70 years.[20]

In our study of chemotherapy in oesophago-gastric cancer there were no significant differences in the incidence of CTC grades 3 and 4 toxicity between the two age cohorts. However, this analysis must be interpreted with caution as the majority of older patients receiving platinum-containing therapy were aged 70–74 years, and none were 80 years of older. Furthermore, there are two indicators of more frequent moderate severity toxicity in older patients. First, there was a statistically non-significant trend in the frequency of early cessation of platinum-containing treatment in older patients. Second, patients ⩾70 years received 5-FU at a significantly lower dose intensity than younger patients.

The absence of increased toxicity with increasing age is consistent with the findings of some analyses in colorectal cancer, whilst differing from others. The Royal Marsden Hospital series found no difference in grade 3–4 toxicity in patients receiving palliative chemotherapy.[10] In contrast, a higher incidence of grade 3–4 stomatitis was observed in elderly patients with adjuvant chemotherapy (19% v 11%; $P = 0.02$). A second analysis detected no increased incidence of grade 3–4 nausea or vomiting, stomatitis or diarrhoea with increasing age in patients receiving adjuvant chemotherapy.[21] However, leucopenia increased from 4% to 8% in older patients ($P < 0.05$). Furthermore, the same group detected an increased incidence of grade 3 overall toxicity, diarrhoea, stomatitis and infection in patients aged 65 years and older receiving palliative 5-FU chemotherapy.[22] An analysis of two randomised trials comparing capecitabine with bolus 5-FU and leucovorin reported an increased incidence of grade 3–4 toxicity in older patients.[23] In addition, it was recognized that impaired renal function was associated with capecitabine-induced toxicity.[23] Renal function frequently declines with increasing age. Therefore, a regression analysis was performed with the result that no independent impact of age in addition to reduced creatinine clearance was found. 5-FU tolerability impaired in these trials at least to a similar degree as reduced renal function. This might be the cause of the increased grade 3 toxicity in elderly patients described in the

pooled analysis of four North central Cancer Treatment Group trials. [22]

As with fluoropyrimidines, irinotecan as second-line monotherapy results in an increase in grade 3/4 neutropaenia (22% vs. 35%; $P = 0.228$).[12] However the incidences of infection, fever and febrile neutropaenia did not increase with age. In addition, there was a similar incidence of grade 3–4 diarrhoea in the two age cohorts (16% vs. 15%).

As other studies have previously concluded in relation to the treatment of colorectal cancer in the elderly, we conclude that patients $\geqslant$70 years that fulfill the standard inclusion criteria of clinical trials have the same advantage from chemotherapy for oesophago-gastric cancer as patients <70 years. The older patients did not experience an excess of severe toxicity. We acknowledge that patients $\geqslant$70 years are underrepresented amongst patients with metastatic disease receiving platinum-based chemotherapy regimens due to physician selection. Nonetheless, age alone is not a contra-indication for the selection of patients for chemotherapy treatment in oesophago-gastric cancer. Elderly patients without significant co-morbidities should be treated with the same regimens and included in the same trials as younger patients.

Conflict of interest statement

None declared.

REFERENCES

1. Statistics NCfH: Leading causes of death and numbers of deaths, according to age: United States, 1980 and 2001 (updated on 1/5/2004); 2004. Available from: http://www.cdc.gov/nchs/data/hus/tables/2003/03hus032.pdf.
2. Statistics NCfH: Chartbook on Trends in Health of Americans, Health United States. US Departmen of Health and and Human Services, Centers for Disease Control and Prevention; 2003. p. 17–88.
3. The Population, The State of the Health in the European Community in 2000. Brussels, European Union; 2000. p. 2–12.
4. Yanick R, Ries L. Aging and cancer in America: demographic and epidemiologic perspectives. *Haematol Oncol Clin North Am* 2000;**14**:17–23.
5. Glimelius B, Ekstrom K, Hoffman K, et al. Randomised comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 1997;**8**:163–8.
6. Pyrhonen S, Kuitunen T, Nyandoto P, et al. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. *Br J Cancer* 1995;**71**:587–91.
7. Murad A, Santiago F, Petroianu A, et al. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer* 1993;**72**:37–41.
8. Lewis J, Kilgore M, Goldman D, et al. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol* 2003;**21**:1383–9.
9. Hutchins L, Unger J, Crowley J, et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999;**341**:2061–7.
10. Popescu R, Norman A, Ross P, et al. Adjuvant or palliative chemotherapy for colorectal cancer in patients 70 years or older. *J Clin Oncol* 1999;**17**:2412–8.
11. Folprecht G, Cunningham D, Ross P, et al. Efficacy of 5-fluorouracil-based chemotherapy in elderly patients with metastatic colorectal cancer: a pooled analysis of clinical trials. *Ann Oncol* 2004;**15**:1330–8.
12. Chau I, Norman A, Cunningham D, et al. Elderly patients with fluoropyrimidine and thymidylate synthase inhibitor-resistant advanced colorectal cancer derive similar benefit without excessive toxicity when treated with irinotecan monotherapy. *Br J Cancer* 2004.
13. Chau I, Norman A, Cunningham D, et al. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer-pooled analysis from three multicenter, randomised, controlled trials using individual patient data. *J Clin Oncol* 2004;**22**:2395–403.
14. Louvet C, Carrat F, Mal F, et al. Prognostic factor analysis in advanced gastric cancer patient treated with hydroxyurea, leucovorin, 5-fluorouracil and cisplatin (HLFP regimen). *Cancer Invest* 2003;**21**:14–20.
15. Polee M, Hop W, Kok T, et al. Prognostic factors for survival in patients with advanced oesophageal cancer treated with cisplatin-based combination chemotherapy. *Br J Cancer* 2003;**89**:2045–50.
16. Rougier P, Ducreux M, Mahjoubi M, et al. Efficacy of combined 5-fluorouracil and cisplatinum in advanced gastric carcinomas. A phase II trial with prognostic factor analysis. *Eur J Cancer A* 1994;**30**:1263–9.
17. Tebbutt N, Norman A, Cunningham D, et al. A multicentre, randomised phase III trial comparing protracted venous infusion (PVI) 5-fluorouracil (5-FU) with PVI 5-FU plus mitomycin C in patients with inoperable oesophago-gastric cancer. *Ann Oncol* 2002;**13**:1568–75.
18. Ross P, Nicolson M, Cunningham D, et al. Prospective randomised trial comparing mitomycin, cisplatin and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin and PVI 5-FU in advanced esophagogastric cancer. *J Clin Oncol* 2002;**20**:1994–2004.
19. Webb A, Cunningham D, Scarffe H, et al. Randomised trial comparing epirubicin, cisplatin and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997;**15**:261–7.
20. Chau I, Norman A, Cunningham D, et al. Elderly patients with fluoropyrimidine and thymidylate synthase inhibitor-resistant advanced colorectal cancer derive similar benefit without excessive toxicity when treated with irinotecan. *Br J Cancer* 2004;**91**:1453–8.
21. Sargent D, Goldberg R, Jacobson S, et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. *N Engl J Med* 2001;**345**:1091–7.
22. Jacobson S, Cha S, Sargent D, et al. Tolerability, dose intensity, and benefit of 5FU-based chemotherapy for Advanced Colorectal Cancer (CRC) in the elderly. A North Central Cancer Treatment Group (NCCTG) study. *Proc Am Soc Clin Oncol* 2001;**20**:1534 [[abstract]].
23. Cassidy J, Twelves C, Van Cutsem E, et al. First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. *Ann Oncol* 2002;**13**:566–75.