

ORIGINAL ARTICLE

Treatment decision plans matter in elderly patients with gastrointestinal cancer: suboptimal or optimal?

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Summary

Purpose: Aging is an important risk factor for cancer. Molecular changes and defective immunity associated with aging result in increased susceptibility to many carcinogens of the gastrointestinal system (GIS). Comorbidities and changes in drug metabolism in elderly patients make the treatment of GIS cancers difficult.

Methods: Between January 2009 and December 2012, a total of 790 patients diagnosed with GIS cancers were retrospectively evaluated. Among them, 357 patients aged ≥ 65 years constituted the study population in which the patient characteristics, disease location, TNM stage, ECOG PS, co-morbidities, chemotherapy regimens and overall survival (OS) were assessed.

Results: The patient median age was 71 years (range 65–94). Cancer localizations were colorectal cancer (CRC), gastric cancer, and the pancreaticobiliary system (PBS) cancer in 178 (49.9%), 124 (34.7%), and 55 (15.4%) patients, respectively. A total of 260 (69%) patients underwent chemotherapy: 167 (64.3%) patients received optimal chemotherapy, and 93 (35.7%) suboptimal chemotherapy.

The median OS was 47, 14, and 11 months in CRC, gastric, and PBS cancers, respectively. OS was better in the optimally-treated group than in the suboptimally-treated group among patients with all types of cancer. OS was 67 vs 19 months ($p<0.001$), 17 vs 8 months ($p=0.004$), and 12 vs 10 months ($p=0.46$) in CRC, gastric, and PBS cancers in the optimal and suboptimal chemotherapy groups, respectively. Multivariate analysis showed that the disease stage in all cancer types and optimal chemotherapy in the CRC group were important predictors of survival ($p<0.001$ and $p=0.021$, respectively).

Conclusion: Cancer is usually in advanced stage at the time of diagnosis in these elderly patients and screening programs might improve outcomes in this age group. Patients with GIS cancers (especially CRC and gastric cancer) should be encouraged to receive optimal chemotherapy regimens.

Key words: elderly, gastrointestinal system cancers, survival, treatment

Introduction

The correlation between aging and an increased risk of cancer is well known. Almost 60% of the total cancer population is over 65 years of age, although this older population comprises only 12% of the total population worldwide [1-3]. This increased risk with age is more prevalent in GIS cancers. The peak age of the development of GIS cancers is in the sixth

and seventh decades [4-6].

Elderly patients have decreased immunity and increased susceptibility to certain carcinogens. Environmental carcinogens result in DNA hypomethylation and genetic instability. Other changes, such as shortening of telomeres, reduced telomerase activity, and activation of the p16 antioncogene, may oppose carcinogenesis. The duration of exposure to these carcinogens is also important for cancer development [7].

Treatment of elderly patients with cancer is so complex that multidisciplinary approaches are needed. Aging is associated with a progressive decrease in organ function, survival expectation, and stress tolerance, and treatment alternatives are uncertain in older patients. Furthermore, elderly patients are usually excluded from clinical cancer trials and have not been given opportunities for representation in certain pivotal clinical trials. Thus, knowledge about treatment efficacy and safety in elderly patients with cancer is insufficient [8].

In this retrospective analysis, we aimed to study the effect of treatment plan decisions on OS in elderly patients over 65 years of age with CRC, gastric cancer, and PBS cancer.

Methods

A retrospective study of 790 patients who were diagnosed with GIS cancers and admitted to two tertiary hospitals in Turkey between January 2009 and December 2012 was performed. This study was approved by the Ethics Committee of the Abant Izzet Baysal University Faculty of Medicine. Patient characteristics, cancer location, TNM staging, Eastern Cooperative Oncology Group (ECOG) performance status (PS), co-morbidities, treatment schedules, and survival data were evaluated. The clinicopathological data were collected through examination of the patient medical charts and computer records. Information on OS was obtained from hospital medical records or a database of the general directorate of population and citizenship affairs. A chemotherapy regimen was classified as optimal if it was strongly recommended by guidelines and given at the recommended dosage and frequency and as suboptimal if it was less strongly recommended by guidelines or the dosage or frequency were modified.

Statistics

A statistical analysis was performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY). Descriptive statistics are presented as minimum–maximum for discontinuous variables and as number and percent (%) for nominal variables. OS was calculated from the date of diagnosis to the date of death from any cause or the date of last contact. Patient survival was estimated using the Kaplan–Meier method. The log-rank test was used to compare and analyze the survival data. The determination of independent prognostic factors influencing survival was performed using the Cox proportional hazards model. The 95% confidence interval was calculated for all hazard ratios (HRs) in the Cox regression analysis. A *p*-value <0.05 was considered statistically significant.

Results

We were able to reach the medical records of 790 patients diagnosed with a GIS cancer in both study Centers during the aforementioned time period. Among these, 357 (45.1%) patients aged ≥ 65 years constituted the study population. Their median age was 71 years (range 65–94). Of these, 131 (36.7%), 122 (34.2%), 68 (19%), and 36 (10.1%) patients were aged 65–69, 70–74, 75–79, and >80 years, respectively.

The numbers of male and female patients were 217 (60.8%) and 140 (39.2%), respectively. Cancer localizations were colo-rectum, stomach, and PBS in 178 (49.9%), 124 (34.7%), and 55 (15.4%) patients, respectively. Of the whole study population, a total of 170 (47.6%) patients had metastatic disease on admission, and the liver was the primary site of metastasis, diagnosed in 134 (37.5%) patients. ECOG PS was 1 in 216 (60.5%) patients. Hypertension and coronary heart disease were common co-morbidities, occurring in 139 (38.9%) patients. The basic demographic characteristics of the patients are shown in Table 1.

A total of 260 (69%) patients received chemotherapy. Among all patients, 25 (6.6%), 36 (9.5%), and 56 (14.9%) did not receive chemotherapy because of early-stage disease, a low ECOG PS, and refusal to undergo chemotherapy, respectively. As classified above, 167 (64.3%) patients received optimal chemotherapy, and 93 (35.7%) patients received suboptimal chemotherapy, as shown in Table 2. Optimal and suboptimal (reduced-dose regimen) chemotherapy according to stage and tumor site is displayed in Table 3.

The median OS was 47, 14, and 11 months in patients with CRC, gastric cancer, and PBS cancer, respectively (Figure 1). OS was better in the optimal-treatment group than in the suboptimal-treatment group in patients with all types of cancer. OS was 67 vs 19 months ($p < 0.001$), 17 vs 8 months ($p = 0.004$), and 12 vs 10 months ($p = 0.46$) in patients with CRC, gastric cancer, and PBS cancer in the optimal and suboptimal chemotherapy groups, respectively (Figures 2–4). The 1-, 2-, and 3-year OS of patients are shown in Table 4.

The determination of independent prognostic factors influencing survival using the Cox proportional hazards model showed that after correction, disease stage was the predominant factor affecting survival. The survival of stage 4 patients was 5-fold worse than that of stage 3 patients ($p < 0.001$). Suboptimal chemotherapy resulted in 4-fold worse survival than optimal treatment in patients with CRC ($p = 0.021$) (Table 5).

Table 1. Demographic characteristics of elderly gastrointestinal system cancer patients

Characteristics	Gastric cancer N (%)	Colorectal cancer N (%)	Pancreaticobiliary cancer N (%)	Total N (%)
Age, years median (range)	70 (65-89)	72 (65-94)	71 (65-89)	71 (65-94)
Sex				
Male	91 (73.4)	97 (54.5)	29 (52.7)	217 (60.8)
Female	33 (26.6)	81 (45.5)	26 (47.3)	140 (39.2)
Stage				
1	2 (1.6)	5 (2.8)	1 (1.8)	8 (2.3)
2	12 (9.7)	33 (18.5)	5 (9.1)	50 (14)
3	42 (33.9)	77 (43.3)	10 (18.2)	129 (36.1)
4	68 (54.8)	63 (35.4)	39 (70.9)	170 (47.6)
Metastasis				
None	56 (45.2)	115 (64.6)	16 (29.1)	135 (37.8)
Liver	59 (47.6)	44 (24.7)	31 (56.4)	134 (37.5)
Lung	0	6 (3.4)	2 (3.6)	8 (2.2)
Bone	1 (0.8)	2 (1.1)	1 (1.8)	4 (1.1)
Brain	0	2 (1.1)	0	2 (0.6)
Multiple	8 (6.5)	9 (5.1)	5 (9.1)	22 (6.2)
ECOG PS				
1	63 (50.8)	127 (71.3)	26 (47.3)	216 (60.5)
2	45 (36.9)	44 (24.7)	23 (41.8)	112 (31.4)
3	16 (12.9)	7 (3.9)	6 (10.9)	29 (8.1)
Co-morbidity				
None	54 (43.5)	62 (34.8)	19 (34.5)	135 (37.8)
HT+CAD	42 (33.9)	81 (45.5)	16 (29.1)	139 (38.9)
DM	10 (8.1)	7 (3.9)	8 (14.5)	25 (7)
DM+HT+CAD	16 (12.9)	26 (14.6)	12 (21.8)	54 (15.1)
COPD	1 (0.8)	1 (0.6)	0	2 (0.6)

ECOG PS: Eastern Cooperative Oncology Group performance status, HT: hypertension, CAD: coronary artery disease, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease

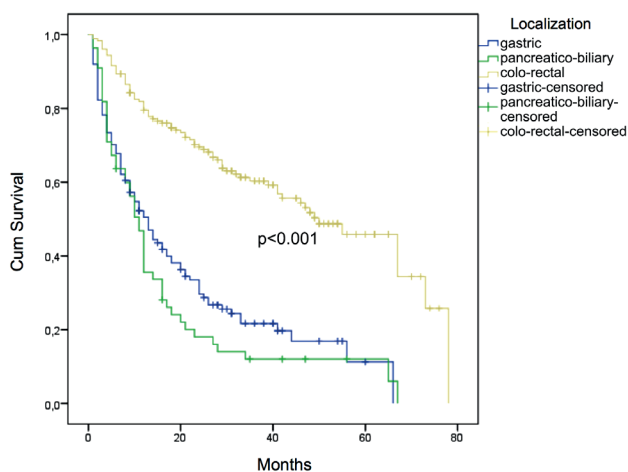
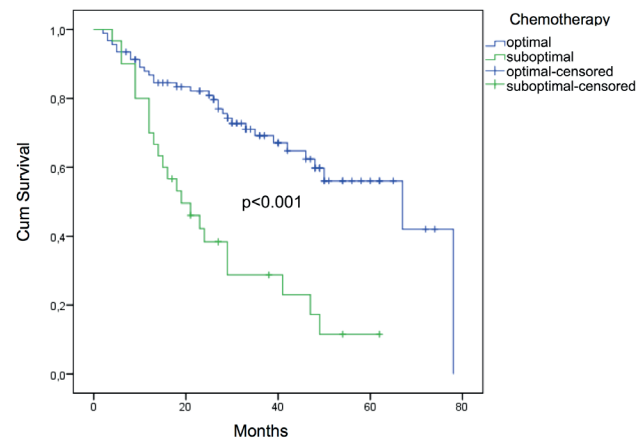
**Figure 1.** Patient overall survival curves according to cancer localization.**Figure 2.** Overall survival according to the chemotherapy regimens of patients with colorectal cancer.

Table 2. Classification of the treatments received by elderly patients according to the localizations of their GIS cancer

	Gastric cancer N (%)	Colorectal cancer N (%)	Pancreaticobiliary cancer N (%)	Total N (%)
Early stage	4 (3.2)	20 (11.2)	1 (1.8)	25 (6.6)
Low ECOG PS	16 (12.9)	7 (3.9)	6 (10.9)	36 (9.5)
Unwilling to chemotherapy	17 (13.7)	29 (16.3)	5 (9.1)	56 (14.9)
Suboptimal chemotherapy	39 (31.4)	30 (16.9)	20 (36.4)	93 (24.7)
Optimal chemotherapy	48 (38.8)	92 (51.7)	23 (41.8)	167 (44.3)
Total	124	178	55	357

ECOG PS: Eastern Cooperative Oncology Group performance status

Table 3. Chemotherapy regimens according to stage of patients with gastric cancer, colorectal cancer and pancreaticobiliary cancer

Chemotherapy regimens	Gastric cancer			Colorectal cancer			Pancreaticobiliary cancer		
	Stage 2 N (%)	Stage 3 N (%)	Stage 4 N (%)	Stage 2 N (%)	Stage 3 N (%)	Stage 4 N (%)	Stage 2 N (%)	Stage 3 N (%)	Stage 4 N (%)
DCF			8 (20.5)						
DCF*			10 (25.5)						
Cis-Cape			10 (25.5)						
Cis-Cape*			11 (28.5)						
FUFA	10 (100)	20 (52.6)		18 (100)					6 (20.0)
FUFA*		18 (48.4)					2 (25)		6 (20.0)
FOLFOX4				57 (79.2)		10 (31.2)			
FOLFOX4*				10 (13.8)		9 (28.1)			
Cape-Ox						7 (21.8)			
Cape-Ox*				5 (7.0)		6 (18.9)			
Gemcitabine							5 (100)	2 (25)	10 (33.4)
Gemcitabine*								4 (50)	8 (26.6)
Total	10 (100)	38 (100)	39 (100)	18 (100)	72 (100)	32 (100)	5 (100)	8 (100)	30 (100)

DCF: Docetaxel, cisplatin and 5-fluorouracil, Cis-Cape: cisplatin and capecitabine, FUFA: 5-fluorouracil and folinic acid, FOLFOX-4: folinic acid, oxaliplatin and 5-fluorouracil, Cape-Ox: capecitabine and oxaliplatin. * dose reduction applied (suboptimal treatment)

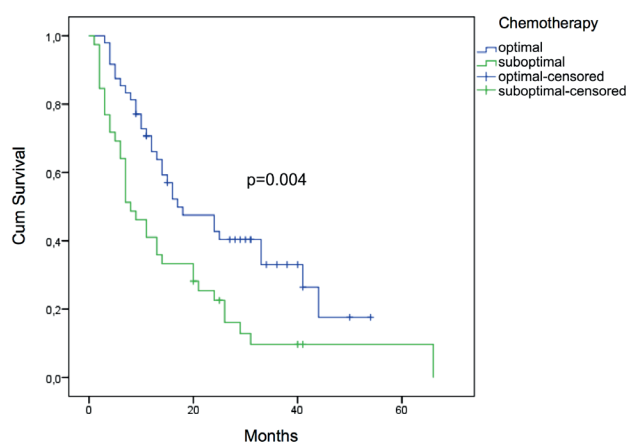
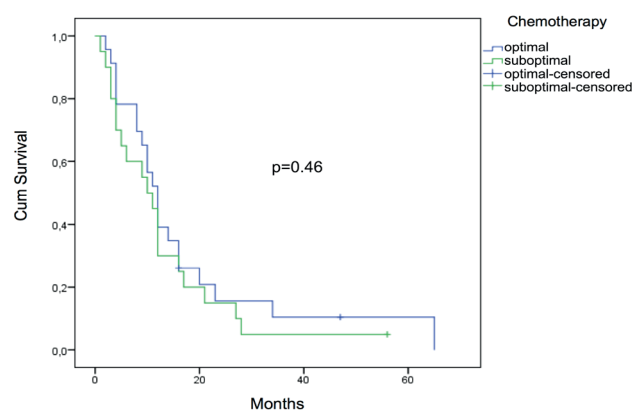
**Figure 3.** Overall survival according to the chemotherapy regimens of patients with gastric cancer.**Figure 4.** Overall survival according to the chemotherapy regimens of patients with pancreaticobiliary cancer.

Table 4. Overall survival according to treatments received

Variables	Survival (%)				Median overall survival (95% C.I.)	p-value
	N	1 year	2 years	3 years		
Gastric cancer					14 (10.1-17.9)	
Optimal chemotherapy	48	70	47.5	33	17 (7.7-26.2)	0.004
Suboptimal chemotherapy	39	41	22	9	8 (4.6-11.4)	
Colorectal cancer					47 (39.8-56.2)	
Optimal chemotherapy	92	86	82	69	67 (35.6-98.4)	<0.001
Suboptimal chemotherapy	30	70	38	28	19 (10.3-27.7)	
Pancreaticobiliary cancer					11 (9.2-12.7)	
Optimal chemotherapy	23	52	15	10	12 (9.7-14.3)	0.46
Suboptimal chemotherapy	20	45	15	5	10 (5.6-14.4)	

Table 5. Evaluation of effective risk factors for overall survival by multivariate Cox proportional hazard regression analysis

Variables	Relative risk	95% Confidence interval		p-value
		Lower limit	Upper limit	
Sex	1.269	0.906	1.777	0.166
Age	0.989	0.955	1.025	0.549
ECOG PS				
2	0.734	0.339	1.588	0.432
3	5.948	0.764	46.293	0.089
Stage				
3	1.537	0.720	3.283	0.267
4	5.426	2.543	11.577	0.001
Co-morbidity	0.923	0.642	1.328	0.667
Chemotherapy				
Gastric	0.975	0.279	3.408	0.968
Colorectal	4.831	1.274	18.318	0.021
Pancreaticobiliary	2.960	0.246	35.637	0.393

ECOG PS: Eastern Cooperative Oncology Group performance status

Discussion

The incidence of cancer is 60% in patients older than 65 years of age, and the mortality rate is almost 70% worldwide in this age group [8,9]. Older populations have been increasing in Western countries, leading to an increase in the number of patients with cancer [10]. The increase in the incidence of cancer is more prevalent in patients with GIS cancers. More than half of patients with gastric cancer and CRC are over 70 years of age [11]. In the present analysis, nearly half of patients with GIS cancers were over 65 years of age.

Malaise, fatigue, and lack of appetite are common chronic symptoms limiting patients' activity. These symptoms are more frequent in older than

in younger patients with the same disease. These symptoms are also seen in otherwise healthy elderly people because of decreased organ function, decreased neuromuscular energy production, and prevalent depression. Furthermore, some symptoms of cancer are attributed to senility. Hence, a diagnosis of cancer is often delayed in elderly patients [12-14]. For example, anemia is more common in otherwise healthy elderly people and is often ignored as an urgent symptom of cancer [15].

One study showed that two-thirds of elderly patients with gastric cancer had unresectable disease on admission to the hospital, leading to decreased survival, and the 5-year OS was 15.2% in elderly patients with advanced gastric cancer [16].

In the present analyses we also found that most patients in all disease groups were admitted with stage 4 disease, leading to decreased survival in our study population.

Elderly patients with cancer are such a heterogeneous group that chronological age is not sufficient information for creating a treatment plan [2]. Chemotherapy may not provide good results in frail patients. This may make the physician uncertain about the treatment plan. However, most patients are at an intermediate state, neither fit nor frail. Thus, personalization of treatment for elderly patients with cancer is suggested [8,17]. Assessment of physiological age with comprehensive geriatric assessment, adjustment of chemotherapy doses to patients, and symptom management are necessary for the treatment of elderly patients with cancer [2]. Pharmacodynamic changes and increased susceptibility to side effects of some chemotherapeutics, such as neurotoxicity or mucositis, can be easily addressed. Thus, aging itself is not a contraindication to cancer treatment [2,10,18]. Because of the fear of age-related toxicity of chemotherapy, elderly patients with gastric cancer may receive modified or suboptimal cytotoxic regimens despite the fact that they could have tolerated more aggressive treatment regimens [11]. Parallel to this finding, our study showed a difference in OS between elderly patients with gastric cancer who received suboptimal compared with optimal treatment.

There is a tendency in clinical studies to give less chemotherapy to elderly patients with CRC than to their younger counterparts. As the age of

a patient increases, adjuvant chemotherapy use dramatically decreases. In one study, adjuvant chemotherapy was decreased in elderly patients with stage III colon cancer or stage II or III rectal cancer. In another study, 88% of patients younger than 55 years received chemotherapy compared with only 48% of those aged 75–84 years [19,20]. Another study showed that chemotherapy in elderly patients resulted in survival benefit as in younger patients despite of lower doses of chemotherapy in CRC patients [21].

Parallel to this finding, we also found that suboptimal treatment was associated with decreased survival. Elderly patients should be treated in a multidisciplinary setting to maintain their clinical status throughout the treatment course [4,11].

Management of GIS cancers varies significantly by primary site, age, and comorbidities [4]. GIS cancers are mostly diagnosed late in older patients because fatigue, debility, and anorexia are common symptoms in both patients with GIS cancers and those with senility. Thus, screening programs for older patients are important. In the CRC group, optimal chemotherapy schedules, despite inferior chemotherapy options, resulted in increased survival. Thus, older patients with CRC should be encouraged to undergo optimal chemotherapy regimens. Physiological conditions and co-morbidities are more important than age in determining treatment strategies. However, because survival was rarely increased with any type of chemotherapy in these elderly patients with gastric and PBS cancer, clinical studies may reveal better options.

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