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REVIEW ARTICLE

What are the optimal treatment modalities according to age group in gastric cancer patients?

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Summary

Cancer in older people has become an increasingly common problem due to the prolonged life expectancy of the general population. Cancer treatment is challenging but it can be more difficult in geriatric population. Aging is associated with progressive reduction of the body's functional capacity and increased prevalence of chronic diseases. As a result, cancer treatment could cause higher prevalence of serious side effects. In the literature there are only sparse studies about treatment modalities in geriatric gastric cancer patients, therefore our aim was to review the literature concerning this topic and reach a sound conclusion.

Key words: *age group, gastric cancer, geriatric patients, optimal management, outcome, treatment modality*

Introduction

The incidence and mortality rates of most cancers are decreasing in the United States and in other developed Western countries [1,2]. However, cancer still accounts for more deaths than heart diseases in those aged 85 years and younger [3]. Cancer in older people has become an increasingly common problem due to prolonged life expectancy of the general population.

The overall incidence of gastric cancer and the mortality rates are decreasing worldwide, but despite the recent decline, gastric cancer remains the fourth most common cancer and the second leading cause of cancer-related mortality [4-6]. Moreover, the incidence of gastric cancer increases with age, especially in the United States, and most gastric cancer patients in Japan are older than 60 [7,8]. The age-adjusted mortality rate due to gastric cancer has been reported to increase with age [9].

In the literature there are only few reports about treatment modalities of geriatric gastric cancer patients. Because studies related to this topic are rather sparse, the aim of this article was to review the relevant literature reports and search for a sound conclusion.

Methods

We searched PubMed and Cochrane databases using the following keywords: "gastric cancer treatment" and/or "gastric cancer treatment for older age people". The searched reports were written in English.

Results

Kim et al. [10] reported that the elderly (>70 years) and young (<36 years) patients had similar distributions with respect to depth of invasion, nodal involvement, hepatic metastasis, peritoneal dissemination, tumor stage at the initial diagno-

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sis, and type of surgery. Elderly patients (mean 73.3±3.1 years) especially had a well or moderately well differentiated histology, while young patients (mean 30.6±5.1 years) had a poorly differentiated histology and signet ring cell carcinoma, and the 5-year overall survival (OS) rates of elderly or young patients did not differ statistically.

However, Tural et al. [11] demonstrated that the median age at diagnosis and the percentage of elderly patients with gastric cancer were increased in their patient population. Both the elderly and non-elderly patients had similar histopathological features and underwent similar surgical modalities. The elderly patients had lower OS survival rates than the non-elderly patients, but only fewer of elderly patients underwent adjuvant treatment or palliative chemotherapy, contrary to the non-elderly group (Table 1).

There are numerous studies in the literature related to gastric cancer treatment in older patients. Generally, the choice of treatment is surgery, but it seems that surgery plus postoperative chemoradiotherapy is a better option. In a study with 556 patients [12], patients were randomly assigned to surgery alone or surgery plus postoperative chemoradiotherapy (25 mg fluorouracil/m^2/day, plus 20 mg leucovorin/m^2/day, for 5 days). Median age for the surgery-alone group was 59 years (range 23-80) and for the surgery plus chemoradiotherapy group it was 60 years (range 25-87). Older age was not an exclusion criterion for this study. The results showed that chemoradiotherapy after gastric cancer resection significantly improved relapse-free and OS [12].

In another study [13] patients having gastrectomy with extended (D2) lymph node dissection were randomly assigned to chemotherapy with S-1 or to follow-up. In the S-1 group, drug administration was started within 6 weeks after surgery and continued for 1 year. The treatment regimen consisted of 6-week cycles in which, in principle, 80 mg of oral S-1/m^2/day was given for 4 weeks and no chemotherapy was given for the following 2 weeks. The primary end point was OS. This trial showed that 3-year OS rates were 80.1 and 70.1% for patients treated with S-1 or surgery alone, respectively (p=0.003). Results concerning elderly patients were not statistically significant compared with non-elderly patients.

Surgery is one of the treatment options but it is also debatable. Surgical technique was scrutinized in some studies. The two largest of these studies [14,15] have found similar 5-year OS rates after D1 and D2 procedures (35% and 33%, respectively, in a study conducted in the United Kingdom [14] and 45% and 47%, respectively, in a study in the Netherlands) [15]. Both trials found significantly increased in-hospital mortality related to the distal pancreatectomy and splenectomy performed as part of the D2 procedure. In subgroup analysis, patients with N2 stage have had better OS. In the British Cooperative trial [16], there wasn't any difference between D1 and D2 dissection but D2 caused more morbidity and mortality. On the other hand, two different studies showed no relation between D2 dissection and OS or morbidity [17,18]. In a prospective phase 2 study, following D2 dissection morbidity and mortality rates were much lower compared with previously published randomized clinical trials and similar to Japanese figures [19]. D2 dissection seems to have a confounding effect on survival but several authors reported that this was due to the stage of disease rather than the treatment itself [20-22].

In two meta-analyses, D2 dissection had a positive effect regarding locoregional recurrence, especially in T3 and T4 tumors [23,24] but in these studies patients with T1 and T2 tumors had also D2 dissection. Subgroup analysis of patients with positive lymph node status and intestinal type gastric cancer showed that chemoradiotherapy was more effective [23,24].

In NCCN 2014, it is recommended that gastrectomy with D1 dissection or modified D2 dissection with at least 15 lymph node removed should be done and should be performed in D2 dissection expert center [25].

As age gets older, surgery can cause concerns with regard to morbidity and mortality, but Maehara et al. concluded that age alone was not a contraindication to extensive surgery because there was no increase in operative morbidity and mortality rates from analysis of 344 patients with gastric cancer aged 70 years or older. Similarly, there was no difference between elderly and non-elderly patients in terms of postoperative mortality in this study [26]. Takeda et al. recommended that standard radical lymph node dissection should be used for tumors extending through the serosa (T3) and/or involving extragastric lymph nodes (N2), even in patients aged 80 years or more [27].

Surgical treatment can cause high morbidity and mortality, and its effect on prognosis is obscure at some points. In a study with 2773 patients, 51% of the patients had surgery. For patients aged 0-59,60-69,70-79 and 80 years and over, resection rates were 64, 55, 54 and 35%, respectively. The postoperative mortality risk increased markedly

Table 1. Treatment modality and outcome in elderly and non-elderly patients

Study	*Design*	*Location/ year*	*Total no. of patients*	*Study population & aim*	*Stages*	*Elderly group (no. of patients)*	*Main results for elderly*
Tural et al. [11]	retrospective	Turkey/2012	866	To investigate age-specific incidence rates and to compare disease stage, treatment, and survival according to age group; >70 years (n=151) vs ≤70 years (n=715)	Non-metastatic (surgery+) : 386 Metastatic : 480	Group1: >70years (n=151) Group2: ≤70years (n=715)	1 and 5-year survival in non-metastatic elderly was lower than in the younger (p=0.015, p=0.03). Adjuvant and palliative CT rates were significantly less in the elderly (p=0.02 , p=0.007)
Sakuramoto et al. [13]	prospective phaseIII	Japan/2007	1034	To compare OS, RFS and to assess safety and adverse effects of S-1. Adjuvant with S-1 group (n=515) vs Surgery only (BSC) group (n=519)	IB:1 II:264 IIIA:170 IIIB:54 IV:40 IB:0 II:282 IIIA:157 IIIB:56 IV:35	70-80 years; S-1 (n=130) vs Surgery only (n=117)	No difference for age subgroups
Takeda et al. [27]	retrospective	Japan/1994	1516	To compare outcomes of surgery in elderly with younger patients; Group1 (n=56)(>=80 years) vs Group2 (n=373)(70-79years) vs Group3 (n=1087)(<70 years)	63% of resected cases had advanced cancer	≤70 years (n=429)	5-year survival rates for resected cases were similar in patients <70 years and 70-79 years (68% and 68%), but lower in patients ≥80 years (47%)
Damhuis et al. [28]	prospective	Netherlands/ 1995	2773	To study resection rates and postoperative mortality in gastric cancer patients; ≥70 years (n=1697) vs <70 years (n=1076)	Of resected patients I:382 II:323 III:465 IV:176 X(insuff data):45	≤70 years (n=1697)	Resection rates were lower (45% vs 58%) while postoperative mortality was higher (12.4% vs 3.4%) in elderly
Saito et al. [29]	retrospective	Japan/2006	1473	To investigate the prognostic significance of age; <70 years (n=1119) vs >70 years (n=354)	I:59.4% II:15.3% III:20.8% IV:4.5% I:61% II:11% III:22.6% IV:5.4%	>70 years (n=354)	10-year survival was lower (70.2% vs 81.4% p<0.001), while postoperative mortality rates were higher non (significantly) in elderly (3.2% vs 2.0%)
Endo et al. [30]	retrospective	Japan/2013	90	To assess survival after surgery in very elderly patients according to their clinical characteristics; Curative resection group (n=58) vs BSC group (n=32)	I:26 II:19 III:13 I:18 II:11 III:3	All patients (n=90) ≥85 years	OS (p=0.006) was significantly better in the curative resection group in patients aged 85-89 years. But curative resection did not affect OS in ≥90 years (p=0.24)
Endo et al. [31]	retrospective	Japan/2011	56	To review the prognoses of patients aged 85 years and older; Surgery (n=36) vs BSC (n=20) in ≥85 years	I:14 II:12 III:10 I:9 II:7 III:2	All patients (n=56) ≥85 years	OS (p=0.0078) was better in surgery group
Kitamura et al. [34]	retrospective	Japan/1996	1600	To determine the clinicopathological features of gastric cancer in the elderly; <39 years (n=86) vs 40-69 years (n=1134) vs ≥70 years (n=380)		≥70years (n=380) (23.7%)	5-year survival rate was lower (p< 0.05) in the elderly group than the middle-aged group; 44.6% vs 57.1%

Continued on next page

Liang et al. [35]	prospective	China/2013	920	To elucidate the prognostic value of age and identify the optimal treatment for elderly. Younger group (age < 50 years) (n=166) vs Middle-aged group (50-69 years) (n=481) vs Elderly group (≥ 70 years) (n=273)	I:11.4% II:27.1% III:51.2% IV:10.2 I:8.9% II:28.1% III:54.9% IV:8.1% I:7.7% II:26.4% III:62.6% IV:3.3%	≥70 years (n=273)	≥ 70 years demonstrated a significantly lower 5-year OS rate than the younger and middle-aged patients (elderly vs middle-aged vs younger patients, 22% vs 36.6% vs 38%, respectively) (p=0.03). Limited LN dissection (D1 resection) is appropriate and postoperative CT is possibly unnecessary for elderly patients. CT was a prognostic factor for the younger and middle-aged, but not for the elderly patients
Lee et al. [37]	randomized multicenter phaseII	Korea/2008	96	To investigate the activity and safety of two oral fluoropyrimidines, capecitabine or S-1, in elderly patients with advanced gastric cancer (AGC); Capecitabine (n=46) vs S-1 (n=45)	All patients were metastatic	All patients (n=96) ≥65	ORR, TTP and OS were similar
Jatoi et al. [38]	Pooled analysis of 8 consecutive, first-line trials	USA/2010	367	To investigate whether elderly do as well with CT as their younger counterparts, in patients with metastatic esophageal, gastroesophageal, and gastric cancer; ≥65 years (n=144) vs <65 years (n=213)	All patients were metastatic	≥65 years (n=144)	Rates of grade 3+ adverse events (fatigue, neutropenia, renal failure, infection, stomatitis, hypotension) were higher among elderly patients (p<0.05)

CT:chemotherapy, LN:lymph node, BSC:best supportive care, OS:overall survival, TTP:time to progression, ORR:overall response rate, RFS:relapse-free survival

after the age of 70 years; for patients under 70 years of age, the rate was 3.4% compared with 12.4% for those aged 70 years and older. These results indicated that surgical treatment can be performed even in elderly patients at an acceptable risk, and palliative resections may be considered especially in patients younger than 70 years [28]. In another study [29],1473 patients were retrospectively analyzed. All patients had undergone distal partial, proximal partial or total gastrectomy with regional dissection of group 1 (D1), 2 (D2), or 3 (D3) lymph nodes. They also had received chemotherapy: tegafur (FT-207; TAIHO, Tokyo, Japan) and uracil–tegafur (UFT)(TAIHO) were used in 425 and 141 patients, respectively. Patients were classified as elderly if they were older than 70 years and as non-elderly if they were younger than 70. The results showed that lymph node dissection was limited and chemotherapy was administered in a more conservative way in elderly patients. Ten-year survival rates were 70.2% (95% CI 64.2–76.3) and 81.4% (95%CI 79.0-83.8) in elderly and non-elderly patients [29].

In the literature there are two studies involving 85-year and older patients. Gastric cancer patients aged ≥85 years were retrospectively reviewed in a study [30]. OS was significantly better in the curative resection (OP) group than in the BSC (best supportive care) group in females (hazard ratio/HR 0.27, 95% CI 0.12-0.57, p<0.001) but not in males (HR 0.71, 95% CI 0.35-1.49, p=0.35). OS was significantly better in the OP group in patients aged 85-89 years (HR 0.44, 95% CI 0.25-0.78, p=0.006) but not in patients aged ≥90 years (HR 0.47, 95% CI 0.12-1.66, p=0.24). OS was significantly better in the OP group in patients with stage IB-IIIC cancer (HR 0.29, 95% CI 0.14-0.58, p<0.001) but not in patients with stage IA cancer

(HR 0.52, 95% CI 0.21-1.27, p=0.15). There were no significant differences in clinical characteristics between 58 patients with curative resection and 32 patients with BSC group in cancer stage IA-IIIC and with ECOG performance status of 0-3. As a result, female patients aged 85-89 years, and patients with stage IB-IIIC cancer had significantly better OS with surgery than without. For male patients aged ≥90 years or with stage IA, the decision to perform surgery should be carefully made and BSC might be an prefered strategy. In another study [31] with 117 patients aged 85 years and older, 36 cases underwent curative resection and 30 cases received BSC, after excluding those in stage IV. The clinical characteristics of the surgery group (n=36) and BSC group (n=20) were statistically identical, and the OS was significantly better in the surgery group (p=0.0078). As a conclusion, postoperative outcomes were characterized as relatively acceptable. Surgery may be feasible and beneficial even for extremely aged patients (85 years and older), except for those with ECOG performance status of 4.

In a prospective, multicenter, open label, randomized phase III study irinotecan was compared with BSC to evaluate the impact of second-line chemotherapy on survival [32]. Forty patients with gastric or gastro-esophageal junction adenocarcinoma with locally advanced or metastatic stage were enrolled during or within 6 months after first-line chemotherapy. Patients had ECOG performance status 0–2 and objectively determined tumor progression. In arm A, median age was 58 years (range 43-73), and irinotecan 250 mg/m^2 q3w (first cycle) was given, to be increased to 350 mg/m^2, depending on toxicity. In arm B, median age was 55 years (range 35-72), and only BSC was given. No objective response in arm A was noted while SD (53%) and PD (47%) were registered. Improvement of tumor-related symptoms was seen in 50% in arm A and 7% in arm B. The HR for death was reduced to 0.48 (95% CI 0.25-0.92) in the irinotecan arm (p=0.012). Median survival in arm A was 4.0 months (95% CI 3.6-7.5), and in arm B it was 2.4 months (95% CI 1.7-4.9). In this study irinotecan as second-line chemotherapy significantly prolonged OS compared to BSC [32].

Another treatment option is adjuvant chemotherapy. In a study with 896 patients, 214 received the XELOX regimen, 48 received FOLFOX-6 and 634 patients were subjected to surgery alone without chemotherapy [33]. OS was compared. FOLFOX-6 had equal efficacy to the XELOX regimen (capecitabine/oxaliplatin), which improved 3-year disease-free survival (DFS) in the CLASSIC study (adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy). Both chemotherapy regimens were significantly associated with improved survival after D2 dissection compared to D2 dissection alone, regardless of age, tumor differentiation and nodal status. But in this study [33] subgroup analysis according to age wasn't done and patients older than 75 years were not included. On the other hand, in another study 380 patients older than 70 years were enrolled, in which the postoperative mortality (within 30 days) was higher in the elderly (>70 years) than in the middle-aged (40-60 years) patients [34]. A same aged patient group (as elderly patients) was compared to a younger group in another study [35]. Patients (n=920) were categorized into three subgroups: younger group (age<50 years), middle-aged group (50-69 years), and elderly group (≥70 years). There were no significant differences in OS between D1 and D2 resection for patients aged ≥ 70 years (5-year OS: 23.1% for D1 and 19.8% for D2, p=0.232), although those aged <70 years could benefit from D2 resection. Improved survival with chemotherapy was observed only in the younger and middle-aged patients, and elderly patients benefited little from chemotherapy. In this study, FOLFOX-6 was administered and radiotherapy was not used.

In a randomized, open-label, phase III study, irinotecan was compared with paclitaxel in patients with advanced gastric cancer [36]. Patients were randomly assigned to receive either paclitaxel (80 mg/m^2 on days 1, 8, and 15, every 4 weeks) or irinotecan (150 mg/m^2 on days 1 and 15, every 4 weeks). The primary end point was OS, and secondary end points were progression-free survival (PFS), response rate, adverse events, and the proportion of patients who received third-line chemotherapy. This study included 219 patients were enrolled. Median PFS was 3.6 months in the paclitaxel group and 2.3 months in the irinotecan group (HR 1.14; 95% CI, 0.88-1.49; p=0.33). Response rate was 20.9% in the paclitaxel group and 13.6% in the irinotecan group (p= 0.24). Common grade 3 to 4 adverse events were neutropenia (paclitaxel group, 28.7%; irinotecan group, 39.1%), anemia (21.3%; 30.0%), and anorexia (7.4%; 17.3%). No statistically significant difference was observed between paclitaxel and irinotecan for OS and both were reasonable second-line treatment options for advanced gastric cancer [36].

In another randomized multicenter phase II trial from Korea, capecitabine and S-1 were com-

pared as first-line treatment in elderly patients. Elderly (≥ 65 years) chemo-naive patients with advanced gastric cancer were randomly assigned to receive capecitabine 1250 mg/m^2 twice daily on days 1–14 every 3 weeks or S-1 40–60 mg/m^2 twice daily 1–28 every 6 weeks. Ninety-six patients from 9 centers were enrolled; 49 were assigned to receive capecitabine and 47 S-1. Overall response rate (the primary end point) was 27.2% (95% CI, 14.1–40.4, 12 of 44 assessable patients) with capecitabine and 28.9% (95% CI, 15.6–42.1, 13 of 45) with S-1. Median time to progression and OS in the capecitabine arm (4.7 and 9.5 months, respectively) were similar to those in the S-1 arm (4.2 and 8.2 months, respectively). The incidence of grade 3–4 granulocytopenia was 6.8% with capecitabine and 4.8% with S-1. Grade 3–4 non-hematologic toxicities were: asthenia (9.1% with capecitabine vs 7.1% with S-1), anorexia (6.8 vs 9.5%), diarrhea (2.3 vs 0%), and hand–foot syndrome (6.8 vs 0%) more frequently found in the capecitabine arm. In conclusion both capecitabine and S-1 monotherapies were active and tolerable as first-line treatment for elderly patients with gastric cancer [37].

When compared to younger population, adverse effects can be seen frequently in older population. In a study, 367 patients from 8 first line trials were included, and adverse events were compared in patients with >65 years old vs <65 years. Chemotherapy regimens included i) etoposide + cisplatin; ii) 5-fluorouracil + leucovorin; iii) 5-fluorouracil + levamisole; iv) irinotecan; v) docetaxel + irinotecan; vi) oxaliplatin + capecitabine; vii) docetaxel + capecitabine; and viii) bortezomib + paclitaxel + carboplatin. The primary end point was the rate of grade 3 or worse adverse events. At the end, adverse events were observed more frequently in patients older than 65 years. If the age cut off was changed to 70 years, the difference disappeared. However, age-related OS difference was not statistically significant [38]. In another study [39], 502 patients were enrolled, and chemoradiotherapy was administered to 66.5% of young vs 51% to old patients; chemotherapy alone was administered to 27.5 vs 42% and adjuvant radiotherapy alone was administered to 6% vs 7%. In young patients the main cause of death was advanced disease and in older patients it was associated with co-morbid conditions. Another study included 482 patients with a previously untreated gastric cancer, who had undergone surgery [40]. Fifty-six patients in this group were under 50 years of age, and the remaining 367 patients constituted the reference group. Gastrectomy was the treatment of choice in both groups. This was performed on 66% of the young patients and on 58% of the reference group. There were considerable differences between the two groups with regarding to postoperative complications. The rate of anastomotic leak was higher, though not significantly, in patients over 50 years at 5%, compared with 2% in the younger group (p>0.05). The rate of general complications of a cardio-pulmonary nature was 11% in the over-50-year-old patients compared with 2% in the younger group, which was significant (p=0.018). There was a major difference in hospital mortality. The mortality rate for the older patients was 5%, while none of the younger patients died in hospital. This difference was clear but did not quite reach statistical significance. Regarding the long-term survival, the under-50s again showed significantly better results. The 5-year OS rate was 68% in younger patients, compared with 45% in the older reference group (p=0.041).When the long-term OS of the two groups was considered, after dividing them into the different tumor stages, it was clear that there were major differences in favor of the younger patients at all tumor stages, although significance was only reached in stage I. Postoperative survival was markedly (but not significantly) longer in the younger patients with stage III disease (54% compared with 28%, p=0.12).

In conclusion, in gastric cancer treatment, generally, surgery plus chemoradiotherapy have positive results. Although there are some controversies between studies' results, gastric cancer treatment related side effects are more frequently seen in elderly patients compared to younger population. On the other hand, if general health and performance status are good and co-morbidities are not serious, geriatric patients benefit to the same degree as younger patients do. Although there is not a consensus for gastric cancer treatment in geriatric patients, all modalities can be used as in young population patients since the results are encouraging. In this context patient-based decision making should be done. Treatment side effects and patient co-morbidities can cause more serious problems than cancer itself.

Conflict of interests

The authors declare no confict of interests.

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