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Outcomes by treatment modality in elderly patients with localized gastric and esophageal cancer

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ABSTRACT

Background We aimed to assess current treatment patterns and outcomes in elderly patients with localized gastric and esophageal (GE) cancers.

Methods This retrospective analysis considered patients 75 years of age or older with GE cancers treated during 2012–2014. Patient demographics and tumour characteristics were collected. Overall survival (OS) and disease-free survival were assessed by univariable and multivariable Cox proportional hazards regression, adjusting for demographics. Logistic regression analyses were used to examine factors affecting treatment choices.

Results The 110 patients in the study cohort had a median age of 81 years (range: 75–99 years). Primary disease sites were esophageal (55%) and gastric (45%). Treatment received included radiation therapy alone (29%), surgery alone (26%), surgery plus perioperative therapy (14%), chemoradiation alone (10%), and supportive care alone (14%). In multivariable analyses, surgery (hazard ratio: 0.48; 95% confidence interval: 0.26 to 0.90; $p = 0.02$) was the only independent predictor for improved OS. Patients with a good Eastern Cooperative Oncology Group performance status ($p = 0.008$), gastric disease site ($p = 0.02$), and adenocarcinoma histology ($p = 0.01$) were more likely to undergo surgery.

Conclusions At our institution, few patients 75 years of age and older received multimodality therapy for localized GE cancers. Outcomes were better for patients who underwent surgery than for those who did not. To ensure optimal treatment selection, comprehensive geriatric assessment should be considered for patients 75 years of age and older with localized GE cancers.

Key Words Elderly patients, geriatric assessments, gastric cancer, esophageal cancer, treatment selection

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INTRODUCTION

In part because of an aging population, the incidence of cancer is expected to increase by 67% in people 65 years of age and older from 2010 to 2030[1]. Although cancer is typically a disease of the elderly, no cut-off age has been universally accepted for defining "elderly," although 65 years is the accepted age in most high-income countries. The National Institute on Aging at the U.S. National Institutes of Health classifies elderly patients into three categories: the "young old" (65–74 years), "older old" (75–85 years), and "oldest old" (>85 years)[2].

Despite the increasing incidence and prevalence of cancer among elderly individuals, that population has been underrepresented in clinical trials[3–5]. For instance, 26% of patients are 75 years of age or older when they are diagnosed with cancer[6], and yet only 10% of that group of patients is enrolled into U.S. National Cancer Institute

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cooperative group clinical trials[7]. Consequently, the safety and efficacy of cancer treatment for elderly patients remain unproven in trials.

Gastric and esophageal (GE) cancers primarily affect an elderly population: median age at diagnosis is 68 and 67 years respectively[6]. Those cancers are also challenging, with a higher mortality rate in elderly (≥65 years) compared with younger (<65 years) patients (21.7 vs. 1.5 per 100,000 for esophageal cancer and 37.1 vs. 3.0 per 100,000 for gastric cancer)[6].

The standard therapy for localized GE cancers is multimodality therapy incorporating chemotherapy, surgery, and radiation. However, as mentioned earlier, patients 75 years of age and older have been underrepresented in the large randomized controlled trials showing an incremental survival benefit with the multidisciplinary approach[8]. In addition, compared with younger patients, elderly patients often have more comorbidities and a poorer performance status, preventing them from receiving optimal standard treatment[9–13]. It has been postulated that the higher mortality rate in elderly patients could in part be related to less-aggressive treatment compared with standard multimodality therapy[9]. However, chronologic age alone cannot be relied on for making treatment decisions because physiology in these patients shows great heterogeneity.

In this retrospective observational cohort study, we evaluated patients 75 years of age and older ("older old" and "oldest old") with localized GE cancers, for whom data about optimal treatment and outcomes are scarce. Given the aging population, it is critical that clinicians understand the benefits and limitations of treatments. Accordingly, our objectives were to assess current treatment patterns in elderly patients with localized GE cancers, to compare survival outcomes, and to identify predictors of treatment selection.

METHODS

Study Population and Data Collection

This retrospective analysis of all patients 75 years of age or older diagnosed with a localized GE cancer who were treated at the Princess Margaret Cancer Centre between 2012 and 2014 included those with adenocarcinoma, squamous cell carcinoma, or mixed adenosquamous carcinoma. Patients with other histologies such as small-cell carcinoma, neuroendocrine tumour, and a hematologic diagnosis were excluded. Patient characteristics including age at diagnosis, sex, Asian ethnicity, and past medical history were collected. The Charlson comorbidity index (CCI)[14] and Eastern Cooperative Oncology Group (ECOG) performance status (PS)[15] at the time of initial presentation were also recorded. Tumour characteristics, including date of diagnosis, histology, pathology staging, and tumour response grade, were collected. In this analysis, adenocarcinoma of the esophagogastric junction types I and II (Siewert classification) were included as esophageal cancer, and type III was defined as gastric cancer. Clinical staging was determined using the 6th edition of the American Joint Committee on Cancer (AJCC 6) staging manual[16]. Notably, patients with T4N1–3M0 gastric cancer are classified as stage IV in AJCC 6, and those patients were included. Treatment details, including intent of treatment, type and date of surgery, chemotherapy regimen, number of cycles of chemotherapy received, and radiation dose and fractionation were collected.

Statistical Analysis

Overall survival (OS) was defined as the time from diagnosis to death from any cause. Disease-free survival was defined as the time from diagnosis to first recurrence or death from any cause. Patients without documented evidence of an event were censored at the date of last follow-up.

The Kaplan–Meier method was used for survival analyses. The log-rank test was used to compare outcomes between treatment groups. Further analyses were performed using univariable and multivariable Cox proportional hazards regression, with adjustment for age, sex, score on the CCI, ECOG PS, AJCC 6 stage, tumour site, histology, and treatment modality received. Logistic regression analyses were used to examine factors affecting treatment choices. Multivariable models using backward selection techniques based on the Akaike information criterion were developed[17]. Median study follow-up was calculated using the reverse Kaplan–Meier estimator. Significance was set at an alpha level of 0.05 for inferential analyses.

This research was reviewed and approved by the Princess Margaret Cancer Centre Research Ethics Board. Written informed consent was waived.

RESULTS

Patient and Treatment Characteristics

Between 2012 and 2014, 854 patients with GE cancers were treated at the Princess Margaret Cancer Centre. Of those patients, 176 (21%) were 75 years of age or older, and 110 (63% of the older group) had localized GE cancer on presentation. Table I presents the patient and disease characteristics. Median age in the group was 81 years (range: 75–99 years), and most were men (n = 81, 74%). At initial presentation, 73% of the patients (n = 80) had an ECOG PS of 0 or 1, and 58% (n = 64) had a score of 0 or 1 on the CCI. Primary sites were esophagus (55%, with 43% squamous histology) and stomach (45%).

Table I also summarizes treatment received, stratified by intent. Treatment intent was decided based on multidisciplinary discussion or patient preference (or both). In our cohort, 53% of the patients (n = 58) underwent curative-intent treatment, with most patients receiving surgery alone (n = 32). Very few patients (n = 26, 24%) underwent bi- or trimodality therapy. The radiation dose for chemoradiation was in the range of 41.4–50 Gy. Although the entire cohort had localized GE cancer, almost half were treated with palliative intent, with most receiving either palliative radiation alone (n = 29, 26%) or supportive care alone (n = 16, 15%).

Survival Outcomes

Median follow-up was 26 months (interquartile range: 11–40 months). Median OS was significantly longer in patients who underwent surgery than in those who did not (Figure 1; 33.1 months vs. 10.3 months; hazard ratio: 0.40; 95% confidence interval: 0.23 to 0.70; p = 0.0015; 1-year

TABLE I Demographics and tumour and treatment characteristics for the study patients

Characteristic	Value
Patients *(n)*	110
Sex [*n* (%)]	
Men	81 (74)
Women	29 (26)
Age (years)	
Median	81
IQR	78–85
Age group [*n* (%)]	
75–85 Years	84 (76)
≥85 Years	26 (24)
Ethnicity [*n* (%)]	
Non-Asian	99 (90)
Asian	11 (10)
Score on the CCI [*n* (%)]	
0	36 (33)
1	28 (25)
2	20 (18)
3	13 (12)
4	10 (9)
≥5	3 (3)
ECOG performance status [*n* (%)]	
0	35 (32)
1	45 (41)
2	17 (15)
3	12 (11)
4	1 (1)
Clinical staging[16] [*n* (%)]	
I	16 (15)
II	37 (34)
III	47 (43)
IV	4 (4)
Undocumented	6 (5)
Tumour characteristics	
Esophageal or GEJ SCC	26 (23)
Esophageal or GEJ adenocarcinoma	35 (32)
Gastric adenocarcinoma	49 (45)
Treatment intent	
Curative	58 (53)
Sx plus perioperative therapy	13 (12)
Sx alone	32 (29)
Definitive chemoradiation or RT	13 (12)
Palliative	31 (28)
RT alone	29 (26)
CTx alone	2 (2)
Unknown	5 (4)
Supportive care	16 (15)

IQR = interquartile range; CCI = Charlson comorbidity index; ECOG = Eastern Cooperative Oncology Group; GEJ = gastroesophageal junction; SCC = squamous cell carcinoma; Sx = surgery; RT = radiation therapy; CTx = chemotherapy.

OS: 75% vs. 39%). Compared with surgery alone, adjunctive treatments (including chemotherapy, radiation therapy, or chemoradiation) added to surgery conferred no associated additional survival benefit (Figure 2; median os: not reached vs. 33.1 months; hazard ratio: 1.03; 95% confidence interval: 0.36 to 2.91; $p = 0.96$). The univariable analyses for os showed that only surgery was significantly associated with better os ($p < 0.001$). Chemotherapy ($p = 0.79$), radiation therapy ($p = 0.24$), and chemoradiation ($p = 0.82$) were not independently associated with os in univariable analyses.

Examining patient characteristics, only age ($p = 0.001$), ECOG PS ($p = 0.04$), and AJCC 6 stage ($p = 0.05$) were significantly associated with os in univariable analyses. In contrast, score on the CCI was nonsignificant ($p = 0.12$). In multivariable analyses to control for the expected confounding factors of patient and disease characteristics (Table II), the beneficial effect of surgery persisted, and apart from clinical stage, surgery was the only independent predictor for improved os ($p = 0.002$).

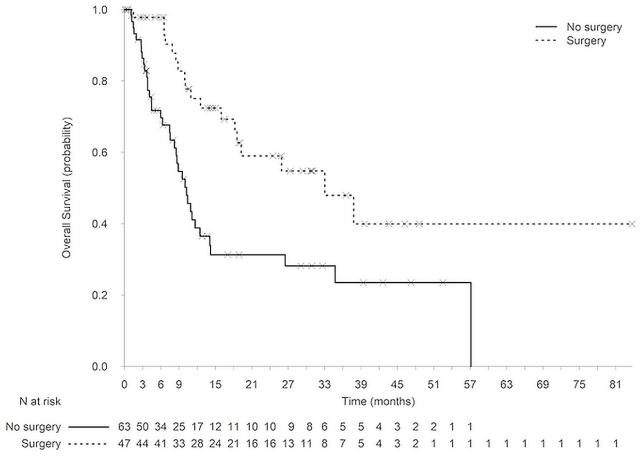

FIGURE 1 Overall survival for patient who did and did not undergo surgery.

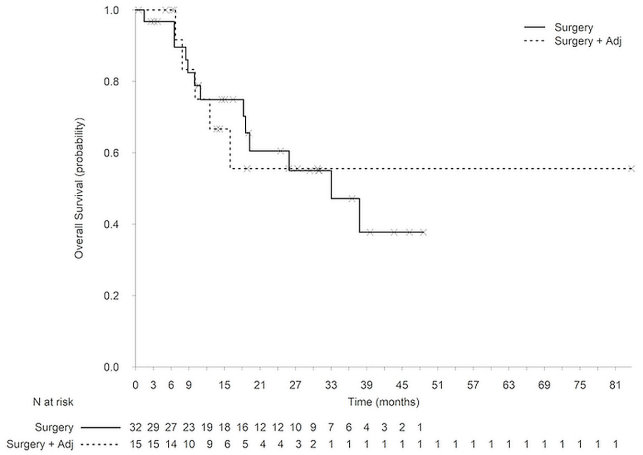

FIGURE 2 Overall survival for patient who underwent surgery alone or surgery and adjunctive therapy (Adj).

Factors Affecting the Treatment Decision

Table III shows the multivariable logistic regression analyses assessing predictors of surgery. Patients with a good ECOG PS, gastric site, and adenocarcinoma histology were more likely to undergo surgery. Neither age nor score on the CCI was found to be a significant predictor of surgery.

DISCUSSION

In this retrospective study, we identified 110 patients 75 years of age or older ("older old" and "oldest old") who presented with localized GE cancers between 2012 and 2014. Despite a median age of 81 years, patients had a relatively good PS, with 80% of patients having an ECOG PS of 0 or 1, and a low comorbidity burden (58% patients had a score on the CCI of 0 or 1). Approximately half the patients (53%) received curative-intent therapy. However, only 14% received standard-of-care therapy (surgery plus perioperative treatment); 10% received definitive chemoradiation. Even though our institute is one of the highest volume cancer centres in Canada, with an established GE cancer multidisciplinary team, treatment of elderly patients was less aggressive—apparently because of concerns about their age and ability to tolerate intensive therapy. Similar trends for less-aggressive management of elderly patients are generally seen in other countries and cancer types, including breast and colorectal cancers[9–13].

Notably, bi- and trimodality therapy were uncommon in the elderly patients in our cohort, who instead underwent mainly curative surgery alone. Notwithstanding patient selection, patients who underwent surgery experienced improved outcomes, having a median OS of 33.3 months compared with 10.3 months for their counterparts who did not undergo surgery. Treatment with surgery had the strongest association with improved OS. As shown in Table III, other variables, including age, ECOG PS, and score on the CCI, likely contributed to OS with relatively less significance and with a lesser magnitude of association. In addition, our study suggests that the incremental benefit from perioperative therapy previously seen in several clinical trials[8,18,19] might be smaller in elderly patients than in younger patients. That hypothesis would have to be validated in prospective randomized controlled trials.

In our study, patients with adenocarcinoma histology or gastric cancer were more likely to undergo surgery. That observation was expected, given that squamous esophageal cancer can be treated with definitive chemoradiation, with favourable outcomes, and surgery can be reserved for salvage[20]. In contrast, chronologic age was not found to be an independent predictor for receipt of surgery, but reassuringly, ECOG PS was a significant predictor. Beyond chronologic age, older adults show great heterogeneity in frailty and comorbidity, requiring careful consideration when making treatment decisions. Patients should not be excluded from treatments, especially surgery, based on chronologic age alone. An earlier study demonstrated that the morbidity and mortality of elderly patients with gastric cancer who underwent surgery was affected by comorbidities rather than by age[21]. In earlier studies, the Comprehensive Geriatric Assessment has been examined to determine factors that affect toxicity and survival and also evaluated as a preoperative assessment tool for cancer patients undergoing surgery[22–24]. For example, after a geriatrician-led Comprehensive Geriatric Assessment, interventions were associated with improved chemotherapy tolerance among cancer patients 70 years of age and older[24], and the assessment was found to be more useful than conventional methods for predicting outcomes in patients 65 years of age or older who undergo elective surgery[22]. A Comprehensive Geriatric Assessment might therefore be a useful tool for evaluating elderly patients with GE cancers to ensure that they are not overlooked for potentially beneficial treatments.

TABLE II Multivariable Cox proportional hazards regression to assess overall survival (model selection by backward elimination)

Variable	Comparison	HR	95% CI	*p* Value[a]
Age	<85 Years vs. ≥85 years	0.54	0.29 to 1.03	0.06
Score on the CCI	<2 vs. ≥2	0.62	0.35 to 1.10	0.10
ECOG PS	<2 vs. ≥2	0.61	0.32 to 1.17	0.14
AJCC stage[b]	I/II vs. III/IV	0.57	0.32 to 1.01	**0.05**
Surgery	Yes vs. no	0.38	0.21 to 0.70	**0.002**

[a] Significant values appear in boldface type.
[b] Greene FL, Page DL, Fleming ID et al., eds. *AJCC Cancer Staging Manual*. 6th ed. Chicago, IL: American Joint Committee on Cancer; 2002.
HR = hazard ratio; CI = confidence interval; CCI = Charlson comorbidity index; ECOG = Eastern Cooperative Oncology Group performance status; AJCC = American Joint Committee on Cancer.

TABLE III Multivariable logistic regression to assess predictors of surgery (model selection by backward elimination)

Variable	Comparison	OR	95% CI	*p* Value[a]
Age	<85 Years vs. ≥85 years	2.49	0.80 to 8.37	0.12
ECOG PS	<2 vs. ≥2	4.56	1.54 to 15.18	**0.008**
Site	Gastric vs. esophageal	3.125	1.17 to 8.33	**0.02**
Histology	Adenocarcinoma vs. SCC	7.69	1.79 to 50	**0.01**

[a] Significant values appear in boldface type.
OR = odds ratio; CI = confidence interval ECOG = Eastern Cooperative Oncology Group performance status; SCC = squamous cell carcinoma.

To our knowledge, the present study is one of the largest to specifically focus on patients 75 years of age or older with localized GE cancer and to describe treatment patterns at a high-volume academic institution. This is an area of need, with a paucity of clinical data to guide management.

Our study has several inherent limitations. First, it is a retrospective study from a single institution within Canada. Given its nonrandomized nature, accounting for all potential confounding factors was difficult. Also, we could not exclude a modest association between variables because the power to detect multiple predictor variables was limited given the number of eligible patients. Second, surgical complication rates, toxicity data, and quality-of-life information could not be accurately procured retrospectively. Finally, the patient population showed significant heterogeneity, with patients being treated with either curative or palliative intent—although we should emphasize that all patients had potentially curable localized GE cancers, and none had metastatic disease at diagnosis.

CONCLUSIONS

At our institution, relatively few patients 75 years of age and older received multimodality therapy for localized GE cancers. Surgery was the only treatment modality that was associated with better survival. To ensure optimal treatment selection, a Comprehensive Geriatric Assessment should be considered for patients 75 years of age or older with localized GE cancers, particularly given the potential benefit of surgery.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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REFERENCES

1. Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J Clin Oncol* 2009;27:2758–65.
2. Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics, 1997. *CA Cancer J Clin* 1997;47:5–27. [Erratum in: *CA Cancer J Clin* 1997;47:68]
3. Hutchins LF, Unger JM, Crowley JJ, Coltman CA Jr, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999;341:2061–7.
4. Trimble EL, Carter CL, Cain D, Freidlin B, Ungerleider RS, Friedman MA. Representation of older patients in cancer treatment trials. *Cancer* 1994;74(suppl):2208–14.
5. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. *J Clin Oncol* 2004;22:4626–31.
6. Howlader N, Noone AM, Krapcho M, *et al.*, eds. SEER Cancer Statistics Review 1975–2014 [archival Web page, based on November 2016 SEER data submission]. Bethesda, MD: U.S. National Cancer Institute, Surveillance, Epidemiology, and End Results Program; 2017. [Available at: https://seer.cancer.gov/csr/1975_2014; cited 14 May 2017]
7. Mooney MM. Older Patients in NCI-Sponsored Clinical Treatment Trials. In: Mooney MM, session leader. Designing Clinical Trials for Older Patients: Regulatory, Community, and Advocacy Perspectives [speaker panel session]. Presented at the 2012 American Society of Clinical Oncology Annual Meeting; Chicago, IL, U.S.A.; 1–5 June 2012. [Video available online at: https://meetinglibrary.asco.org/record/68859/video; cited23 October 2018]
8. Cunningham D, Allum WH, Stenning SP, *et al.* on behalf of the MAGIC trial participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11–20.
9. Steyerberg EW, Neville B, Weeks JC, Earle CC. Referral patterns, treatment choices, and outcomes in locoregional esophageal cancer: a population-based analysis of elderly patients. *J Clin Oncol* 2007;25:2389–96.
10. Anderson SE, Minsky BD, Bains M, Hummer A, Kelsen D, Ilson DH. Combined modality chemoradiation in elderly oesophageal cancer patients. *Br J Cancer* 2007;96:1823–7.
11. DeMichele A, Putt M, Zhang Y, Glick JH, Norman S. Older age predicts a decline in adjuvant chemotherapy recommendations for patients with breast carcinoma: evidence from a tertiary care cohort of chemotherapy-eligible patients. *Cancer* 2003;97:2150–9.
12. Bouchardy C, Rapiti E, Fioretta G, *et al.* Undertreatment strongly decreases prognosis of breast cancer in elderly women. *J Clin Oncol* 2003;21:3580–7.
13. Schrag D, Cramer LD, Bach PB, Begg CB. Age and adjuvant chemotherapy use after surgery for stage III colon cancer. *J Natl Cancer Inst* 2001;93:850–7.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
15. Oken MM, Creech RH, Tormey DC, *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649–55.
16. Greene FL, Page DL, Fleming ID, *et al.*, eds. *AJCC Cancer Staging Manual.* 6th ed. Chicago, IL: American Joint Committee on Cancer; 2002.
17. Akaike H. A new look at the statistical model identification. *IEEE Trans Automat Contr* 1974;19:716–23.
18. Macdonald JS, Smalley SR, Benedetti J, *et al.* Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345:725–30.
19. van Hagen P, Hulshof MC, van Lanschot JJ, *et al.* on behalf of the CROSS group. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074–84.
20. Stahl M, Stuschke M, Lehmann N, *et al.* Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol* 2005;23:2310–17.
21. Charalampakis N, Xiao L, Lin Q, *et al.* Co-morbidities rather than age impact outcomes in patients receiving preoperative therapy for gastroesophageal adenocarcinoma. *Ann Surg Oncol* 2017;24:2291–301.
22. Kim SW, Han HS, Jung HW, *et al.* Multidimensional frailty score for the prediction of postoperative mortality risk. *JAMA Surg* 2014;149:633–40.
23. Owusu C, Berger NA. Comprehensive geriatric assessment in the older cancer patient: coming of age in clinical cancer care. *Clin Pract (Lond)* 2014;11:749–62.
24. Kalsi T, Babic-Illman G, Ross PJ, *et al.* The impact of comprehensive geriatric assessment interventions on tolerance to chemotherapy in older people. *Br J Cancer* 2015;112:1435–44.