Treatments and outcomes of older patients with esophageal cancer: Comparison with younger patients

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Abstract. The number of older patients with esophageal cancer (EC) is increasing due to the population aging and increasing life expectancy. However, no optimal treatment strategy for older patients with EC has been established to date. The aim of the present study was to review and compare the treatment modalities and outcomes of 990 younger and older patients diagnosed with EC in our institution. The patients were divided into younger (≤74 years) and older (≥75 years) groups. The majority of the patients in both groups had early-stage EC and were treated by endoscopic submucosal dissection (ESD). The older patients with locally advanced (stage II and III) EC were more likely to undergo chemoradiotherapy rather than esophagectomy. Among the older patients, 22% selected best supportive care. The disease-specific survival rate of the older patients was significantly lower compared with that of the younger patients, which was likely due to the less intense treatment modalities applied. The prognosis following esophagectomy was significantly better compared with that of chemoradiotherapy in the younger, but not in the older patients. In conclusion, the poorer prognosis of older patients (aged ≥75 years) with stage I EC may improve with multidisciplinary treatment after ESD. Although CRT is currently considered the optimal treatment for older patients with stage II/III EC, more efficient treatment modalities are urgently required.

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Abbreviations: EC, esophageal cancer; ESD, endoscopic submucosal dissection; CRT, chemoradiotherapy; BSC, best supportive care

Key words: esophageal cancer, older patients, treatment outcomes, palliative medicine

Introduction

Esophageal cancer (EC) has a high incidence worldwide (1) and carries a poor prognosis. EC develops mainly in individuals aged >50 years, and the number of older patients with EC in Japan is increasing concomitantly with the aging of the population. Older patients frequently have comorbidities, cognitive decline, polypharmacy and social issues (2). The currently available treatment modalities for EC include endoscopic submucosal dissection (ESD), esophagectomy, radiotherapy, chemotherapy, chemoradiotherapy (CRT) and best supportive care (BSC) (3). ESD was developed for superficial EC restricted to the mucosal layer (T1a) (3). Despite the increasing number of older patients with EC, the majority of clinical trials have involved only, or mostly, younger patients (4). Although some studies have focused on older patients (5), these involved a relatively limited number of subjects and a single arm (6,7). In addition, older patients have high rates of morbidity and mortality (8,9). Therefore, an optimal treatment modality for older patients with EC has yet to be established.

Older patients have been defined as those aged >70, 75 or 80 years, depending on the study in question (6-11). A multicenter questionnaire survey indicated that most institutions consider EC patients aged >75 or 80 years as older patients (12). In the present study, older patients were defined as those who were at least 75 years old.

Patients and methods

Patients. Data on EC patients diagnosed at the Niigata University Medical and Dental Hospital (Niigata, Japan) between January 2007 and December 2017 were retrospectively collected using a hospital-based cancer registry and electronic medical records. The study protocol was approved by the Ethics Review Committee of the School of Medicine of Niigata University (Niigata, Japan; approval no. 2485). All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and National Research Committee and the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards. Patient informed consent was not applicable, as this study was retrospective and data were collected only from

medical records. All patients were informed of the opportunity to opt out of this study through the internet home page of Niigata University School of Medicine. The collected data included age at diagnosis, sex, tumor histology, cancer stage (TNM), treatment modality and prognosis. The Union for International Cancer Control guidelines, version 7 (13), were used for TNM staging. The patient population was divided into younger and older patients, with 75 years at the time of EC diagnosis as the cut-off.

Statistical analysis. The Chi-squared or Fisher's exact tests were used to evaluate the significance of the differences between the two groups. Disease-specific survival duration was defined as the period from the date of diagnosis to that of death due to EC. Patients who died from causes other than EC were censored at the date of death. Surviving patients were censored on the date of their last visit to the hospital. Survival curves were drawn using the Kaplan-Meier method and were compared by log-rank tests. $P<0.05$ was considered to indicate a statistically significant difference. Statistical analyses were performed using IBM version 22.0 (IBM Corp.).

Results

Patient characteristics. A total of 990 patients with EC who visited Niigata University Medical and Dental Hospital between January 2007 and December 2017 were identified. The patient characteristics are summarized in Table I. Of these patients, 359 (36.3%) were aged 75 years or older, and 631 patients (63.7%) were aged <75 years. The median age was 71 years in the entire population, 66 years in the younger group and 79 years in the older group. The majority of the EC patients in both groups had squamous cell carcinoma (90.1%) and early-stage EC (stage 0 or I). The frequency of adenocarcinoma was significantly higher ($P<0.01$), and the rates of different stages were significantly different ($P<0.01$) in the older compared with the younger group.

Treatment modality. Treatment modalities were classified according to the main treatment, as precise classification of treatment modalities would be overly complicated. The majority of the patients underwent ESD (n=629, 63.5%) followed by surgery (n=144, 14.5%) and CRT (n=108, 10.9%) (Table II). Older patients were more likely to undergo radiotherapy alone (n=24, 6.7%) or BSC (n=48, 22%) compared with younger patients ($P<0.01$). The complete multidisciplinary treatment modalities in stage I and II/III cases are presented in Table III. Among younger patients with stage I EC treated by ESD (n=207), 38 (18.4%) also received chemotherapy/radiotherapy, as advanced-stage EC was detected by histological analysis of ESD specimens. By contrast, only 8 (6.5%) of the older patients with stage I EC (n=124) underwent chemotherapy/radiotherapy after ESD. A total of 38 (14.1%) younger patients and 14 (8.2%) older patients underwent surgery with/without additional treatment for stage I disease. Of the younger (n=65) and older (n=21) patients with stage II/III EC who underwent surgery, 46 (71.0%) and 10 (47.6%), respectively, received chemotherapy or/and radiotherapy before or after surgery. Among 10 older patients treated with chemotherapy after surgery, 2 succumbed to treatment-related adverse effects of severe bone marrow suppression.

Although patients with stage IV EC in both groups received various treatment modalities, 40% of the older patients (n=25) underwent BSC ($P<0.01$). Patients with EC of unknown stage were only found in the older group, and 24 (65%) of those opted for BSC.

Disease-specific survival. Disease-specific survival rather than overall survival was analyzed, due to the shorter life expectancy of the older patients. The median follow-up time was 39.6 months (range, 1-120 months). The 5-year disease-specific survival rate was 59.1% in the older group and 75.2% in the younger group at all stages (Fig. 1). The disease-specific survival duration of the older patients was significantly shorter compared with that of the younger patients ($P<0.001$); moreover, the disease-specific survival rate of the older patients decreased markedly after 3.5 years. The disease-specific survival duration of the older patients with stage 0, I or II/III EC was significantly shorter compared with that of the younger patients with stage 0, I or II/III EC (Fig. 1). The disease-specific survival rate of the older patients with stage I EC decreased considerably after 3.5 years, similar to the older group as a whole. The survival curves differed markedly between older and younger patients with stage I and II/III EC compared with those with stage 0 EC. No difference in survival was observed between older and younger patients with stage IV disease.

In older patients with stage II/III EC, the disease-specific survival rate did not differ significantly between patients who underwent surgery and those who received CRT; by contrast, in the younger group, patients who received surgery exhibited a significantly higher survival rate and duration compared with those who were treated with CRT (Fig. 2). Older patients who underwent surgery had a poorer prognosis compared with younger patients. A total of 3 older patients died from adverse events due to chemotherapy for stage II/IIII (2 cases) and IV (1 case) disease; no treatment-related deaths were reported among younger patients.

Discussion

In the present study, the clinicopathological characteristics and treatment modalities and outcomes of 990 patients diagnosed with EC in our institution were reviewed. Compared with younger patients with stage I EC, older patients with stage I EC less frequently received additional treatment following ESD (6.5% of the older vs. 18.4% of the younger patients). Compared with younger patients with stage II/III EC, older patients with stage II/II EC less frequently received perioperative chemotherapy/radiotherapy (47.6 vs. 71.0%, respectively) and definitive CRT (21.7 vs. 34.2%, respectively). Among the older patients, 13% selected BCS compared with 2% of the younger patients. Older patients had a significantly shorter disease-specific survival duration compared with younger patients, specifically for stage I and II/III disease.

Two large studies involving EC patients in the United States and Taiwan (14,15) reported 5-year survival rates of

Table I. Characteristics of patients with esophageal cancer.

Characteristics	Total (n=990)	Age ≤74 years (n=631)	Age ≥75 years (n=359)	P-value
Median age	71 (33-91)	66 (33-74)	79 (75-91)	<0.01
Sex				0.8
Male	853	545	308	
Female	137	86	51	
Histology				<0.01
Squamous cell carcinoma	897	588	309	
Adenocarcinoma	69	32	37	
Others	24	11	13	
Stage				<0.01
0	285	205	80	
I	441	270	171	
II	50	33	17	
III	113	84	29	
IV	64	39	25	
Unknown	37	0	37	

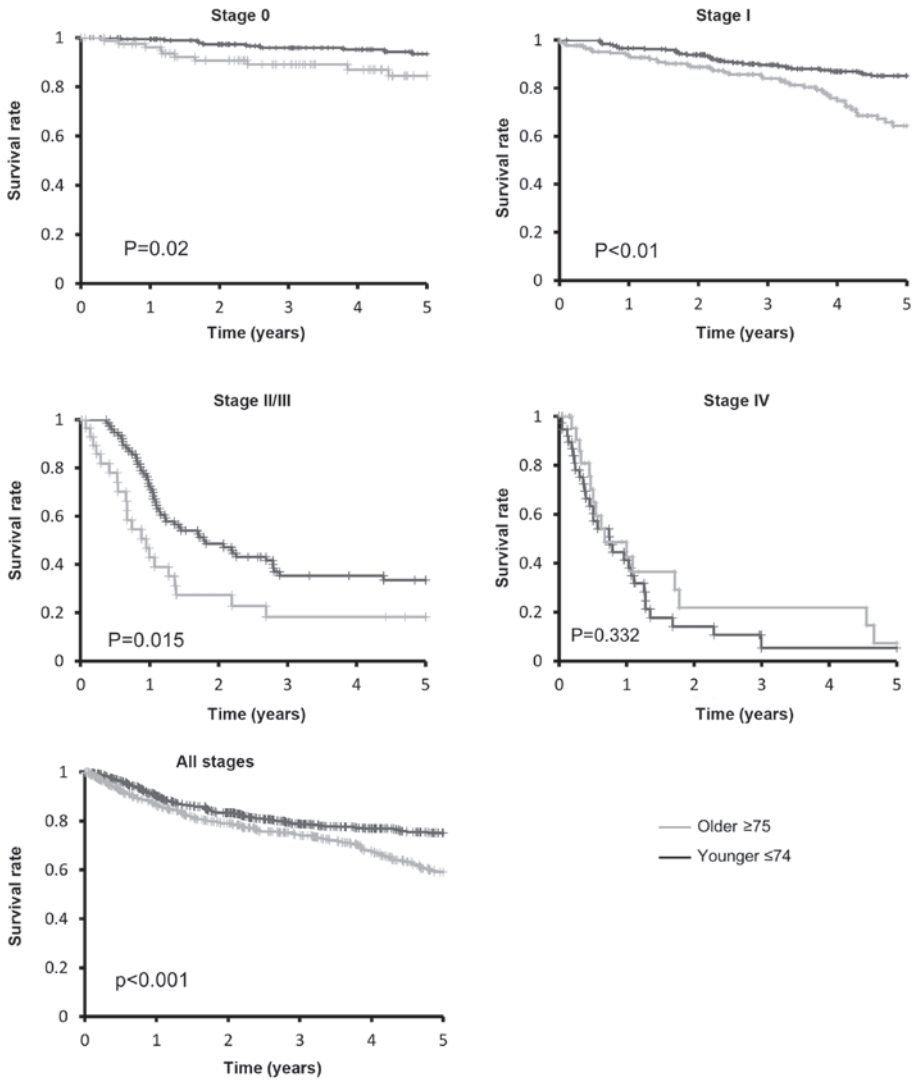

Figure 1. Disease-specific survival according to EC stage. Disease-specific survival of older (n=80) and younger (n=205) patients with stage 0 EC, older (n=171) and younger (n=270) patients with stage I EC, older (n=46) and younger (n=117) patients with stage II/III EC, older (n=25) and younger (n=39) patients with stage IV EC, and older (n=359) and younger (n=631) patients with all-stage EC. EC, esophageal cancer.

Table II. Main treatment modality for each stage of esophageal cancer.

		Patients						
Stage	Modality	Total (n=990)		Age ≤74 years (n=631)		Age ≥75 years (n=359)		P-value
All		N	%	N	%	N	%	<0.01
	ESD	629	63.5	411	65.1	218	60.7	
	Surgery[a]	144	14.5	103	16.3	41	11.4	
	CRT	108	10.9	81	12.8	27	7.5	
	RT	36	3.6	12	1.9	24	6.7	
	Chemotherapy	13	1.3	12	1.9	1	0.3	
	BSC	60	6.1	12	1.9	48	22	
0								<0.01
	ESD	274	96.5	202	98.5	72	90	
	Surgery[a]	1	0.4	0	0	1	1.3	
	CRT	2	0.7	1	0.5	1	1.3	
	BSC	8	2.8	2	1	6	7.5	
I								<0.01
	ESD	331	75.1	207	76.7	124	72.5	
	Surgery[a]	52	11.8	38	14.1	14	8.2	
	CRT	31	7	20	7.4	11	6.4	
	RT	13	2.9	2	0.7	11	6.4	
	Chemotherapy	2	0.5	2	0.7	0	0	
	BSC	12	2.7	1	0.4	11	6.4	
II/III								<0.05
	Surgery[a]	86	52.8	65	55.5	21	45.7	
	CRT	50	30.7	40	34.2	10	21.7	
	RT	11	6.7	3	2.6	8	17.4	
	Chemotherapy	5	3.1	4	3.4	1	2.2	
	BSC	11	6.7	5	4.3	6	13	
IV								<0.01
	Surgery[a]	8	12.5	3	0.1	5	20	
	CRT	26	40.6	21	53.8	5	20	
	RT	11	17.2	6	1.5	5	20	
	Chemotherapy	5	7.8	5	1.3	0	0	
	BSC	14	21.9	4	0.1	10	40	
Unknown	ESD	13	35.1	0	0	13	35.1	<0.01
	BSC	24	64.9	0	0	24	64.9	

[a]Esophagectomy. ESD, endoscopic submucosal dissection; surgery; CRT, chemoradiotherapy; RT, radiotherapy; BSC, best supportive care.

<20%. In addition, older patients (≥70 years of age) were less likely to undergo surgery or/and radiotherapy, and had a lower survival rate. In the US study, 33.1 and 24.0% of the older and younger patients, respectively, opted for BSC (14). These survival rates are lower compared with those reported in the present study, likely because the majority of our patients had early-stage EC, were treated with ESD, and only 13% of the older patients selected BSC.

ESD can completely remove superficial EC and EC confined to the lamina propria mucosae, and is only indicated for Tis and T1a (3,16). Patients diagnosed with T1a (m3) or T1b, i.e., tumor invasion of the muscularis mucosae or submucosal layer, respectively, require adjuvant therapy after ESD.

In a retrospective analysis in an adjuvant treatment setting, both the 3-year relapse-free survival and overall survival rates of patients with T1a (m3) or T1b EC after ESD were significantly improved by adjuvant treatments (17). ESD followed by CRT for stage I [m3(T1a) + T1b] is reportedly effective and safe, and improves the prognosis compared with definitive CRT (18). In the present study, 6.5 and 18.4% of the older and younger patients, respectively, with stage I EC received adjuvant therapy. This low rate of adjuvant treatment may partially explain the marked decrease in the

Table III. Multidisciplinary treatment in stage I and II/III.

Stage	Treatment modalities	Patients			P-value
		Total	Aged ≤74 years	Aged ≥75 years	
I					<0.05
	ESD alone	281	169	116	
	ESD + CRT	41	33	6	
	ESD + RT	7	5	2	
	Surgery[a] alone	34	24	10	
	Surgery[a] + chemotherapy	2	2	0	
	Surgery[a] + CRT	15	12	3	
	Surgery[a] + RT	1	0	1	
	CRT	31	20	11	
	RT	13	2	11	
	Chemotherapy	2	2	0	
	BSC	12	1	11	
II/III					<0.01
	Surgery[a] alone	29	19	11	
	Surgery[a] + chemotherapy	49	38	10	
	Surgery[a] + CRT	8	8	0	
	CRT	50	40	10	
	RT	11	3	8	
	Chemotherapy	5	4	1	
	BSC	11	5	6	

[a]Esophagectomy. ESD, endoscopic submucosal dissection; CRT, chemoradiotherapy; RT, radiotherapy; BSC, best supportive care.

survival rate after 3.5 years among older patients (Fig. 1). Of the 8 older patients who received adjuvant therapy after ESD, 2 (25%) experienced grade 3 or 4 adverse effects of neutropenia, but recovered. Therefore, adjuvant treatments after ESD should be considered for older patients with T1a (m3) and T1b EC. The low rate of surgical treatment (8.2 vs. 14.1%) may also explain the worse prognosis of the older patients.

The prognosis of the older patients with stage II/III EC did not differ significantly between those who underwent surgery and those treated with CRT (Fig. 2). Older patients with EC who received surgery had a poorer prognosis compared with younger patients (Fig. 2). Esophagectomy is a viable alternative treatment option for patients aged >80 years, if the surgical indication is strictly determined (19). In a prior study, the poor prognosis of older patients (aged ≥75 years) who underwent surgery was suggested to be due to the low rate of neoadjuvant chemotherapy (6). Indeed, in the present study, half of the older patients did not receive perioperative therapy, and of the 21 older patients who received adjuvant therapy after surgery, 2 succumbed to treatment-related adverse events. However, the lack of precise data regarding treatment-related complications and cause of death in older patients is a limitation of the present study. CRT is reportedly effective without major toxicity in older patients with locally advanced EC (20). Therefore, CRT may be considered as the optimal treatment strategy for older patients with locally advanced EC.

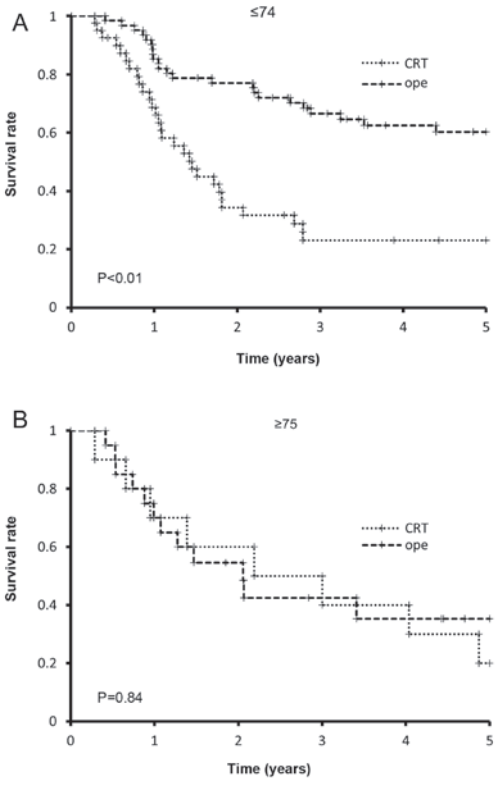

Figure 2. Disease-specific survival of patients with stage II/III EC after surgery and CRT. Disease-specific survival after surgery and CRT of the younger (A) and older (B) patients with stage II/III EC. EC, esophageal cancer; CRT, chemoradiotherapy.

Although 54 and 20% of the younger and older patients, respectively, with stage IV EC were treated with CRT, the median survival duration was 10 months in both groups. CRT should only be considered for patients with tumor-induced esophageal stenosis. Novel and effective treatment modalities for treating metastatic EC, such as immune-checkpoint drugs (21), are required.

In this context, it may be hypothesized that the main explanation for the poorer prognosis in older patients is the more conservative approach to treatment. In addition, the higher frequency of multiple comorbidities among older patients may also partially explain the poorer prognosis in older compared with that in younger patients with EC. However, there was a lack of information regarding comorbidities among EC patients in the present study. Lack of disease-free survival data was also a limitation of this study. A more precise analysis is required to fully elucidate the exact causes of poorer prognosis among older patients.

In conclusion, the poor prognosis of older patients (aged ≥75 years) with stage I EC may be improved with multidisciplinary treatment after ESD. Although the optimal treatment for older EC patients with stage II/III disease may be CRT at present, more efficient and safer treatment modalities, such as immune checkpoint drugs, are urgently needed.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

YM contributed to the drafting of this manuscript. YM, KK, TS, QZ, KS and MM contributed to the collection and analysis of the data. MM and YS contributed to conception, design and editing of the manuscript. All authors have read and approved the final version of this manuscript for publication.

Ethics approval and consent to participate

This study was approved by the Ethics Review Committee of the School of Medicine of Niigata University (no. 2485).

Patient consent for publication

This was a retrospective observational study, carried out by the opt-out method of School of Medicine of Niigata University website.

Competing interests

The authors declare that they have no competing interests.

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