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Differences in treatment and survival between elderly patients with thoracic esophageal cancer in metropolitan areas and other areas

Satoru Motoyama[1,2] | Eri Maeda[3] | Katsunori Iijima[4] | Akira Anbai[5] | Yusuke Sato[1,6] | Akiyuki Wakita[1,6] | Yushi Nagaki[1,6] | Hiromu Fujita[1,6] | Yoshihiro Minamiya[6] | Takahiro Higashi[7]

[1]Division of Esophageal Surgery, Akita University Hospital, Akita, Japan

[2]Department of Comprehensive Cancer Control, Akita University Graduate School of Medicine, Akita, Japan

[3]Environmental Health Science and Public Health, Akita University Graduate School of Medicine, Akita, Japan

[4]Department of Gastroenterology, Akita University Graduate School of Medicine, Akita, Japan

[5]Department of Radiology, Akita University Graduate School of Medicine, Akita, Japan

[6]Department of Thoracic Surgery, Akita University Graduate School of Medicine, Akita, Japan

[7]Division of Health Services Research, Center for Cancer Control and Information Services, National Cancer Center, Akita University Graduate School of Medicine, Akita, Japan

Correspondence
Satoru Motoyama, Department of Comprehensive Cancer Control, Akita University Graduate School of Medicine, 1-1-1 Hondo, Akita, 010-8543, Japan.
Email: motoyama@doc.med.akita-u.ac.jp

Abstract

To address the major issue of regional disparity in the treatment for elderly cancer patients in an aging society, we compared the treatment strategies used for elderly patients with thoracic esophageal cancer and their survival outcomes in metropolitan areas and other regions. Using the national database of hospital-based cancer registries in 2008-2011, patients aged 75 years or older who had been diagnosed with thoracic esophageal cancer were enrolled. We divided the patients into two groups: those treated in metropolitan areas (Tokyo, Kanagawa, Osaka, Aichi, Saitama, and Chiba prefectures) with populations of 6 million or more and those treated in other areas (the other 41 prefectures). Compared were patient backgrounds, treatment strategies, and survival curves at each cancer stage. In total, 1236 (24%) patients from metropolitan areas and 3830 (76%) patients from nonmetropolitan areas were enrolled. Patients in metropolitan areas were treated at more advanced stages. There was also a difference in treatment strategy. The 3-year survival rate among cStage I patients was better in metropolitan areas (71.6% vs. 63.7%), and this finding mainly reflected the survival difference between patients treated with radiotherapy alone. For cStage II-IV patients, there were no differences. Multivariable Cox proportional hazard analysis including interaction terms between treatment areas, cStage, and the first-line treatments revealed that treatments in the metropolitan areas were significantly associated with better survival among patients treated with radiotherapy alone for cStage I cancer. Treatment strategies for elderly patients with thoracic esophageal cancer and its survival outcomes differed between metropolitan areas and other regions.

KEYWORDS

elderly, esophageal cancer, metropolitan, radiotherapy

1 | INTRODUCTION

The rapid transition to a super-aging society has been steadily progressing in Japan, especially in sparsely populated areas. This has prompted reconsideration of the ideal cancer treatment for elderly patients with thoracic esophageal cancer. In 2017, the most recent year for which we have complete data, there were about 25 000 new cases of esophageal cancer in Japan. Among those, more than 40% were 75 years of age or older (Cancer Incidence in Japan 2017. https://www.mhlw.go.jp/content/10900000/000624853.pdf). The most reliable curative treatment for thoracic esophageal cancer, esophagectomy, is highly invasive, and another standard treatment, definitive chemoradiotherapy, is just as burdensome.[1,2] This makes the treatment strategy for elderly patients with thoracic esophageal cancer complicated, as they often have multiple comorbidities and are in comparatively poor physical condition.[3-5] The size of the elderly population varies from region to region in Japan. At present, the elderly make up a majority of the inhabitants in sparsely populated areas, and elderly populations are expected to expand in provincial cities and even metropolitan areas in the near future. In addition, the urban services and medical delivery systems that support elderly patients differ between large metropolitan areas and small provincial cities. It is therefore important to examine the differences in current treatment strategies for thoracic esophageal cancer and their survival outcomes between metropolitan areas and other regions for future perspective. To address these issues, we analyzed the differences in treatment strategies and survival outcomes among elderly patients with thoracic esophageal cancer, taking into consideration cancer stage and comparing between metropolitan areas and other areas.

2 | PATIENTS AND METHODS

This study was approved by the Ethics Committee of Akita University Graduate School of Medicine (No. 2113). We retrieved the 2008-2011 data from the national database of hospital-based cancer registries from the National Cancer Center, Tokyo, Japan.[6] The registry data included the following information on individual cancer patients: (i) clinical profiles, including birth date, sex, tumor topology, and histology code defined by the International Classification of Disease for Oncology, third edition (ICD-O-3); (ii) clinical and pathological tumor-node-metastasis (TNM sixth edition) stage, based on the Union for International Cancer Control (UICC) guidelines; (iii) diagnosis year and month; (iv) first-line treatment provided at the registering facility; and (v) survival information. We extracted the data for patients aged 75 years or older who were diagnosed with thoracic esophageal cancer (ICD-O-3 topography code: C151, C153-155) and treated with some type of anticancer therapy: esophagectomy, chemotherapy, and/or radiotherapy. Patients who received endoscopic treatments were excluded because nearly all patients with early-stage thoracic esophageal cancer treated with curative endoscopic treatment alone have few treatment-related deaths and survive without recurrence after treatment. We adopted the clinical UICC TNM classifications, a pretreatment clinical stage (cStage), tumor invasion depth (cT), node status (cN), and metastasis status (cM) in this study. Survival time was defined as the follow-up time after diagnosis of thoracic esophageal cancer. To ensure its quality, the analyzed survival data were limited to those from facilities able to provide 3-year survival data for all cancers for more than 90% of their patients.

There are three major metropolitan areas in Japan: the Tokyo, Kansai, and Nagoya metropolitan areas. According to the Ministry of Internal Affairs and Communications, these three major metropolitan areas include the cities of the following prefectures. The Tokyo metropolitan area includes the Tokyo, Kanagawa, Saitama, and Chiba prefectures. The Kansai metropolitan area includes the Osaka, Hyogo, Kyoto, Nara, Shiga, and Wakayama prefectures. The Nagoya metropolitan area includes the Aichi, Gifu, and Mie prefectures. Hospital-based cancer registry data are organized by prefecture, not municipality. Among the 47 prefectures, we selected the six in which most of the prefecture is included within a metropolitan area that had a population of 6 million or more as of October 2011 (http://www.stat.go.jp/data/jinsui/2011np/) and defined them as "metropolitan" areas. The other 41 prefectures were defined as "nonmetropolitan" areas. The six metropolitan areas were the Tokyo, Kanagawa, Osaka, Aichi, Saitama, and Chiba prefectures. We then examined the effects of population size and urban function on the treatment of thoracic esophageal cancer in elderly patients.

2.1 | Statistical analysis

We compared metropolitan and nonmetropolitan areas with respect to patient backgrounds and survival curves, taking into consideration cancer stage. Further analyses were performed after dividing the patients based on first-line treatment: esophagectomy with and without preoperative and/or postoperative adjuvant therapy, chemoradiotherapy, chemotherapy alone, and radiotherapy alone. If the group of patients was extremely small, ie, $n < 10$, we presented only the approximate number (0, 1-3, 4-6, 7-9) to avoid identifying personal information according to the rules of hospital-based cancer registries and recommendation from the Ministry of Health, Labor, and Welfare.

Statistical comparisons between two groups were made using Wilcoxon's rank sum test, the chi-squared test, Fisher's test, or Cuzick's Wilcoxon-type test for trend, depending on the type and distribution of the variables. Overall survival was characterized using Kaplan-Meier curves. Survival curves were compared between the two groups using the log-rank test. A multivariable Cox proportional hazards regression model was developed to evaluate the effect of treatment area (metropolitan vs. nonmetropolitan areas) on survival. To account for possible differences in the effect of treatment area on survival among cStages or among the types of first-line treatment, we assessed interaction terms between treatment areas and cStage after stratification based on age, sex, and

first-line treatments in model 1. We further assessed the interaction terms between treatment areas, cStage, and first-line treatments after stratification based on age and sex in model 2. We performed all statistical operations using Stata14-MP (Stata Corp LP).

3 | RESULTS

A total of 5066 patients aged 75 years or older who received cancer treatment, excluding endoscopic treatment, for thoracic esophageal cancer were registered in the hospital-based cancer registry database for 2008-2011. Of those, 1236 (24%) patients were treated in metropolitan areas, while 3830 (76%) were treated in nonmetropolitan areas (Table 1). According to the Statistics Bureau of the Ministry of Internal Affairs and Communications, the population aged 75 years or older in Japan was 14 193 thousand in October 2011, with 4682 thousand (33%) living in metropolitan areas and the remaining 67% living in nonmetropolitan areas. Thus, the proportion of elderly thoracic esophageal cancer patients treated in nonmetropolitan areas (76%) was larger than the proportion of the overall population aged 75 years or older living in those areas (67%).

More than 90% of these patients in both areas were diagnosed with squamous cell carcinoma. Table 1 shows the clinical characteristics of the patients treated in the metropolitan and nonmetropolitan areas. There was a slight but significant difference in age between the two groups (Table 1), and there were significantly fewer patients without lymph node metastasis (cN0) or distant metastasis (cM0) in the nonmetropolitan areas. There were many more patients with advanced (cStage III-IV) cancers in the metropolitan areas than in the nonmetropolitan areas. Esophagectomies were indicated for 30.3% of patients in metropolitan areas, which was more frequent than in the nonmetropolitan areas (27.0%), especially for cStage II cancers (41.9% vs. 33.9%) (Table 1). On the other hand, surgery without adjuvant therapy was indicated more often in nonmetropolitan areas (64.8% vs. 58.6%). For nonsurgical treatment, chemoradiotherapy was indicated more often in nonmetropolitan areas (54.6% vs. 48.3%), while chemotherapy alone was indicated more often in metropolitan areas (15.2% vs. 9.1%). There was no difference in the percentage of patients who received radiotherapy alone between the two groups (36.5% vs 36.3%) (Table 1).

We next evaluated treatment strategies, taking into consideration the cStage. Interestingly, cStage I patients in metropolitan areas received radiotherapy alone significantly more often than those in nonmetropolitan areas (38.6% vs 28.7%); chemoradiotherapy was the predominant treatment in nonmetropolitan areas (35.6%). For cStage II-III patients, esophagectomy was performed more frequently in metropolitan than nonmetropolitan areas (41.4% vs 33.9% in cStage II, 30.9% vs 26.5% in cStage III). In nonmetropolitan areas, chemoradiotherapy was also the predominant treatment for these patients (36.9% of cStage II, 42.8% of cStage III).

The backgrounds of patients aged 80 years or older (n = 2131) were similar in the two groups (Table 2). But although there was no significant difference in the overall rates of esophagectomy in the two groups (19.7% vs 18.0%), for cStage III patients the rate of esophagectomy was higher in metropolitan areas (25.0% vs 17.0%) (Table 2). The rates of surgery without adjuvant therapy did not significantly differ between the groups (72.7% vs 82.9%). For nonsurgical treatment, chemoradiotherapy was more often administered in nonmetropolitan areas (41.9% vs 34.1%), while chemotherapy alone was more often administered in metropolitan areas (10.9% vs 5.1%). There was no difference in the percentage of patients receiving radiotherapy alone in the two groups (55.0% vs 53.0%) (Table 2). Taking cStage into consideration, cStage I patients received radiotherapy much more often in metropolitan areas (74.6% vs 44.4%), while chemoradiotherapy was administered much more often in nonmetropolitan areas (32.4% vs 9.9%). On the other hand, cStage I patients received esophagectomy more frequently in nonmetropolitan areas (21.4% vs 11.3%), whereas cStage III patients received esophagectomy more frequently in metropolitan areas (25.0% vs 17.0%).

Three-year survival rates among cStage I patients were significantly better in metropolitan than nonmetropolitan areas (71.6% vs 63.7%), but there was no difference between the two groups in 3-year survival among cStage II-IV patients (Table 3) (Figure 1). Moreover, among patients who received thoracoscopic esophagectomy, the survival rate was significantly better in metropolitan areas (63.7% vs. 58.0%, $P = .042$). For patients who received radiotherapy alone, the survival rate was also significantly better in metropolitan areas (27.6% vs 20.7%, $P = .006$) (Table 3), especially in cStage I (Figures 2 and 3).

Multivariable Cox proportional hazard analysis (cStage I-IV, n = 4924, model 1) revealed that for cStage I patients, treatment in metropolitan areas was significantly associated with better survival as compared with treatment in nonmetropolitan areas (adjusted HR: 0.76) (95% CI: 0.61-0.94, $P = .011$) (Table 4). In addition, multivariable Cox proportional hazard analysis that included interaction terms between treatment areas, cStage, and the first-line treatments after stratification based on age and sex (cStage I-IV, n = 4924, model 2) revealed that treatment in metropolitan areas was significantly associated with better survival among patients treated with radiotherapy alone for cStage I cancer as compared with treatment in nonmetropolitan areas (adjusted HR: 0.68) (95% CI: 0.49-0.94, $P = .020$) (Table 4).

4 | DISCUSSION

This study revealed that the proportion of elderly patients with more advanced thoracic esophageal cancer was much larger in metropolitan areas and that there were differences in the approaches to treatment between metropolitan and nonmetropolitan areas at different clinical stages. The survival curve for cStage I patients was poorer for patients in nonmetropolitan than metropolitan areas, and this important and serious finding mainly derived from the difference in survival outcomes among patients treated with radiotherapy alone. For cStage I thoracic esophageal cancer, radiotherapy alone was more frequently administered in metropolitan than nonmetropolitan areas

TABLE 1 The characteristics of patients in the metropolitan areas and nonmetropolitan areas (n = 5066)

	Metropolitan areas (n = 1236)		Nonmetropolitan areas (n = 3830)		*P*	
Age (median, IQR)	78	76-81	79	76-82	<.001	1)
Number of males (%)	1043	84.4%	3243	84.7%	.807	2)
Histology						
Squamous cell carcinoma	1179	95.4%	3593	93.8%	.139	3)
Adenocarcinoma	34	2.8%	113	3.0%		
Basaloid squamous cell carcinoma	11	0.9%	47	1.2%		
Neuroendocrine carcinoma	4-6	-	24	0.6%		
Others	7-9	-	53	1.4%		
cT classification						
Tis	1-3	-	4	0.1%	.153	4)
T1	295	23.9%	898	23.4%		
T2	202	16.3%	754	19.7%		
T3	481	38.9%	1446	37.8%		
T4	218	17.6%	587	15.3%		
Tx	37	3.0%	141	3.7%		
cN classification						
N0	457	37.0%	1656	43.2%	<.001	4)
N1	746	60.4%	2045	53.4%		
N2	7-9	-	20	0.5%		
N3	1-3	-	11	0.3%		
Nx	25	2.0%	98	2.6%		
cM classification						
M0	963	77.9%	3083	80.5%	.035	2)
M1	252	20.4%	678	17.7%		
Mx	21	1.7%	69	1.8%		
cStage (UICC)						
cStage 0	1-3	-	4	0.1%	.017	4)
cStage I	233	18.9%	735	19.2%		
cStage II	313	25.3%	1134	29.6%		
cStage III	404	32.7%	1163	30.4%		
cStage IV	257	20.8%	685	17.9%		
Unknown	26	2.1%	109	2.8%		
Treatment						
Esophagectomy	374	30.3%	1033	27.0%	.025	2)
Nonsurgical treatment	862	69.7%	2797	73.0%		
Esophagectomy						
All stages	374	30.3%	1033	27.0%	.025	2)
cStage I	74	31.8%	244	33.2%	.684	2)
cStage II	131	41.9%	384	33.9%	.009	2)
cStage III	125	30.9%	308	26.5%	.084	2)
cStage IV	31	12.1%	73	10.7%	.540	2)
Approach of esophagectomy						
Open thoracotomy	297	79.4%	824	79.8%	.883	2)
Thoracoscopic surgery	77	20.6%	209	20.2%		

(Continues)

TABLE 1 (Continued)

	Metropolitan areas (n = 1236)		Nonmetropolitan areas (n = 3830)		*P*	
Adjuvant therapy (before and/or after surgery)						
No radiation or chemotherapy	219	58.6%	707	68.4%	.005	2)
+Radiation alone	13	3.5%	35	3.4%		
+Chemotherapy alone	107	28.6%	223	21.6%		
+Radiation and chemotherapy	35	9.4%	68	6.6%		
Nonsurgical treatment (all stages)						
Radiation alone	315	36.5%	1016	36.3%	<.001	2)
Chemotherapy alone	131	15.2%	254	9.1%		
Radiation and chemotherapy	416	48.3%	1527	54.6%		
Treatment for cStage I						
Esophagectomy	74	31.8%	244	33.2%	.011	2)
Radiation alone	90	38.6%	211	28.7%		
Chemotherapy alone	7-9	-	18	2.4%		
Radiation and chemotherapy	61	26.2%	262	35.6%		
Treatment for cStage II						
Esophagectomy	131	41.9%	384	33.9%	.066	2)
Radiation alone	74	23.6%	292	25.7%		
Chemotherapy alone	11	3.5%	40	3.5%		
Radiation and chemotherapy	97	31.0%	418	36.9%		
Treatment for cStage III						
Esophagectomy	125	30.9%	308	26.5%	.002	2)
Radiation alone	83	20.5%	282	24.2%		
Chemotherapy alone	45	11.1%	75	6.4%		
Radiation and chemotherapy	151	37.4%	498	42.8%		
Treatment for cStage IV						
Esophagectomy	31	12.1%	73	10.7%	.011	2)
Radiation alone	62	24.1%	175	25.5%		
Chemotherapy alone	63	24.5%	109	15.9%		
Radiation and chemotherapy	101	39.3%	328	47.9%		

Note: Statistical comparisons were made using (1) Wilcoxon's rank-sum test, (2) the chi-squared test, (3) Fisher's exact test, (4) Cuzick's Wilcoxon-type test for trend. If the group of patients was extremely small, ie, n < 10, we present only the approximate number (0, 1-3, 4-6, 7-9).

(38.6% vs 28.7%), and this tendency was more pronounced in patients aged 80 years and older (74.6% vs 44.9%). On the other hand, the survival curves for cStage I patients treated with chemoradiotherapy or esophagectomy did not differ between the two groups. For cStage II-IV patients stratified based on treatment, there was no difference in survival between the two groups for any treatment.

The standard treatment for cStage I thoracic esophageal cancer in nonelderly patients is generally esophagectomy or definitive chemoradiotherapy.[1,2] The International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer was published in 2014.[7] In addition, a meeting of the International Society of Geriatric Oncology was held on the theme of "Bringing two Worlds Together: Oncology and Geriatrics." In elderly cancer patients, there are both age-related physiological changes and psychological problems that must be taken into consideration. These include increased comorbidities as well as cognitive decline and social problems related to family morphology and financial distress. For each patient, the individualization of treatments that can be provided must be considered in the context of risk assessment. As a result, radiotherapy alone became the most frequent treatment for elderly patients with cStage I thoracic esophageal cancer.

What accounts for the difference in the 3-year survival rate among patients treated with radiotherapy alone for cStage I thoracic esophageal cancer? The treatment power of radiotherapy using X-ray appears to be quite sufficient.[8,9] However, the survival curve for those treated with radiotherapy alone was better in metropolitan than nonmetropolitan areas. This raises the possibility that there is a difference in the frequency of radiotherapy-related mortality or adverse events. Moreover, there may also be differences in the patients' health backgrounds that contributed to the difference in survival. It was suggested

TABLE 2 The characteristics of patients aged 80 y or older in the metropolitan areas and nonmetropolitan areas (n = 2131)

	Metropolitan areas (n = 446)		Nonmetropolitan areas (n = 1685)		*P*	
Age (median, IQR)	82	81-84	83	81-85	<.001	1)
Number of males (%)	356	79.8%	1358	80.6%	.714	2)
cT classification						
Tis	1-3	-	1-3	-	.035	3)
T1	89	20.0%	379	22.5%		
T2	80	17.9%	346	20.5%		
T3	183	41.0%	652	38.7%		
T4	78	17.5%	236	14.0%		
Tx	15	3.4%	71	4.2%		
cN classification						
N0	160	35.9%	768	45.6%	<.001	3)
N1	272	61.0%	859	51.0%		
N2	1-3	-	10	0.6%		
N3	1-3	-	1-3	-		
Nx	10	2.2%	45	2.7%		
cM classification						
M0	334	74.9%	1386	82.3%	<.001	3)
M1	104	23.3%	265	15.7%		
Mx	7-9	-	34	2.0%		
cStage (UICC)						
cStage 0	1-3	-	1-3	-	<.001	3)
cStage I	71	15.9%	318	18.9%		
cStage II	111	24.9%	540	32.0%		
cStage III	148	33.2%	499	29.6%		
cStage IV	105	23.5%	268	15.9%		
Unknown	10	2.2%	59	3.5%		
Treatment						
Esophagectomy	88	19.7%	304	18.0%	.413	2)
Nonsurgical treatment	358	80.3%	1381	82.0%		
Esophagectomy						
All stages	88	19.7%	304	18.0%	.413	2)
cStage I	7-9	-	68	21.4%	.052	2)
cStage II	25	22.5%	118	21.9%	.876	2)
cStage III	37	25.0%	85	17.0%	.030	2)
cStage IV	15	14.3%	26	9.7%	.203	2)
Approach of esophagectomy						
Open thoracotomy	77	87.5%	245	80.6%	.136	2)
Thoracoscopic surgery	11	12.5%	59	19.4%		
Adjuvant therapy (before and/or after surgery)						
No radiation or chemotherapy	64	72.7%	252	82.9%	.172	3)
+Radiation alone	4-6	-	15	4.9%		
+Chemotherapy alone	12	13.6%	22	7.2%		
+Radiation and chemotherapy	4-6	-	15	4.9%		
Nonsurgical treatment (all stages)						

(Continues)

TABLE 2 (Continued)

	Metropolitan areas (n = 446)		Nonmetropolitan areas (n = 1685)		*P*	
Radiation alone	197	55.0%	732	53.0%	<.001	2)
Chemotherapy alone	39	10.9%	71	5.1%		
Radiation and chemotherapy	122	34.1%	578	41.9%		
Treatment for cStage I						
Esophagectomy	8	11.3%	68	21.4%	<.001	4)
Radiation alone	53	74.6%	140	44.0%		
Chemotherapy alone	1-3	-	4-6	-		
Radiation and chemotherapy	4-6	-	103	32.4%		
Treatment for cStage II						
Esophagectomy	25	22.5%	118	21.9%	.502	4)
Radiation alone	52	46.8%	229	42.4%		
Chemotherapy alone	4-6	-	13	2.4%		
Radiation and chemotherapy	30	27.0%	180	33.3%		
Treatment for cStage III						
Esophagectomy	37	25.0%	85	17.0%	.049	2)
Radiation alone	49	33.1%	208	41.7%		
Chemotherapy alone	11	7.4%	23	4.6%		
Radiation and chemotherapy	51	34.5%	183	36.7%		
Treatment for cStage IV						
Esophagectomy	15	14.3%	26	9.7%	.008	2)
Radiation alone	39	37.1%	115	42.9%		
Chemotherapy alone	20	19.0%	22	8.2%		
Radiation and chemotherapy	31	29.5%	105	39.2%		

Note: Statistical comparisons were made using (1) Wilcoxon's rank-sum test, (2) the chi-squared test, (3) Cuzick's Wilcoxon-type test for trend, (4) Fisher's exact test. If the group of patients was extremely small, ie, n < 10, we present only the approximate number (0, 1-3, 4-6, 7-9).

that in metropolitan areas, patient selection may be especially rigorous and deeply considered.

From a national survey conducted in 2011 by the Japanese Society of Radiation Oncology, it was determined that 9392 cases of esophageal cancer were treated with radiation at 694 facilities nationwide (JASTRO Database Committee; Japanese Structure Survey of Radiation Oncology in 2011).[10] It was also reported that one or fewer full-time radiation oncologists were employed at 343 facilities (49.4%) and that 290 (38.3%) of the 756 radiation oncologists practiced at facilities in metropolitan areas. The Japanese Radiation Oncology Study Group reported that the treatment results are better at high-volume institutions, and data from 11 major institutions in Japan revealed that there is disparity among institutions.[10] It suggested that differences in the numbers of radiation oncologists and patients may account for the difference in survival outcomes. Furthermore, patients with cStage I esophageal cancer rarely present with symptoms such as dysphagia and are often treated as outpatients. Because radiation monotherapy is less toxic than chemoradiotherapy,[11] it tends to be readily performed, even at facilities that are less familiar with the use of radiotherapy for thoracic esophageal cancer.

The survival curves for patients receiving esophagectomy for cStage I-IV cancers did not differ between metropolitan and nonmetropolitan areas. This is believed to reflect the presence of some degree of centralization of surgical facilities for thoracic esophageal cancer in both metropolitan and nonmetropolitan areas. The reason is that esophagectomy requires considerable technical skill, and the surgical stress on the patients is extremely high. The institute certification system for esophageal surgery by the Japan Esophageal Society has contributed to this moderate centralization.[12-14] Performance of large numbers of esophagectomies (high-volume hospital) has been shown to correlate with better short-term surgical results (mortality or postoperative complication).[15-17] Moreover, a certification system for surgeons and institutes has improved the surgery-related mortality rate and has demonstrated that there is a significantly better 5-year survival rate among cStage II-III thoracic esophageal cancer patients treated with esophagectomy by a board-certified esophageal surgeon at an authorized institute.[12-14]

An attached regional disparity in medical care was that adjuvant therapy before and/or after esophagectomy for advanced thoracic esophageal cancer was more frequent in metropolitan areas. To find the causes will require additional research, and our present data do not provide an answer. It is noteworthy that adjuvant therapy for advanced esophageal cancer is often given in metropolitan areas. Although adjuvant therapy is an essential and standard treatment

TABLE 3 Three-year survival rates (95% confidence interval) among patients who received treatment between two groups

	Overall	Metropolitan areas	Nonmetropolitan areas	*P* (log-rank test)
Number of patients	5066	1236	3830	
Time at risk (d)	4 364 512	1 067 590	3 296 922	
Death	3888 (76.7%)	924 (74.8%)	2964 (77.4%)	
3-y survival rate (%, Kaplan-Meier method)				
Sex				
Female	40.3 (36.8-43.8)	41.0 (33.9-48.0)	40.1 (36.1-44.1)	.464
Male	32.2 (30.8-33.6)	32.1 (29.3-35.0)	32.2 (30.6-33.9)	.449
Age group				
75-79 y old	37.0 (35.3-38.8)	36.7 (33.3-40.1)	37.2 (35.1-39.2)	.476
≥80 y old	28.4 (26.5-30.4)	27.8 (23.6-32.1)	28.6 (26.4-30.8)	.744
cStage				
cStage I (n = 968)	65.6 (62.5-68.5)	71.6 (65.2-76.9)	63.7 (60.1-67.1)	.047
cStage II (n = 1447)	40.4 (37.8-42.9)	41.1 (35.5-46.6)	40.2 (37.3-43.0)	.215
cStage III (n = 1567)	20.9 (18.9 –23.0)	19.8 (16.0-23.9)	21.3 (19.0-23.8)	.717
cStage IV (n = 942)	10.1 (8.2-12.1)	11.1 (7.6-15.4)	9.7 (7.6-12.1)	.320
Treatment				
Esophagectomy (with or without adjuvant therapy) (n = 1407)	47.7 (45.1-50.3)	47.2 (42.0-52.2)	47.9 (44.8-50.9)	.311
Open thoracotomy (n = 1121)	44.8 (41.8-47.7)	43.2 (37.4-48.7)	45.4 (41.9-48.7)	.899
Thoracoscopic surgery (n = 286)	59.5 (53.5-65.0)	63.7 (51.4-73.6)	58.0 (51.0-64.4)	.042
Nonsurgical treatment (n = 3659)	27.9 (26.4-29.3)	27.5 (24.5-30.6)	28.0 (26.3-29.7)	.974
Radiation alone (n = 1331)	22.3 (20.1-24.7)	27.6 (22.7-32.7)	20.7 (18.2-23.3)	.006
Chemotherapy alone (n = 385)	13.8 (10.6-17.6)	12.2 (7.2-18.7)	14.6 (10.6-19.4)	.979
Radiation and chemotherapy (n = 1943)	34.3 (32.2-36.4)	32.1 (27.6-36.7)	34.9 (32.5-37.3)	.249

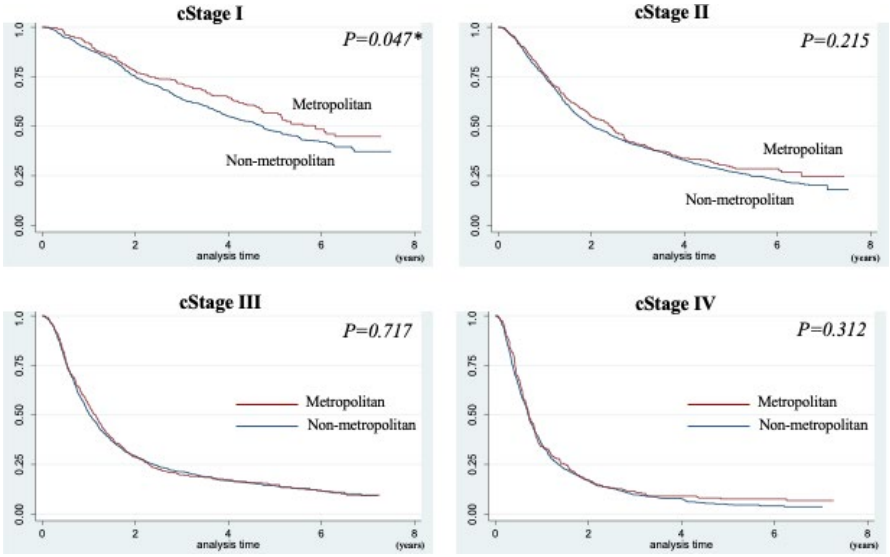

FIGURE 1 Overall survival among patients aged 75 y or more with cStage I, II, III, or IV thoracic esophageal cancer treated in metropolitan and nonmetropolitan areas. The asterisk indicates there is a significant difference in overall survival between cStage I patients in the two areas

for improving postoperative prognosis in advanced thoracic esophageal cancer, administering adjuvant chemotherapy to elderly patients with comorbidities requires experience and skill. This study suggests that assessment of patient risk may have been more accurate in metropolitan areas, but further research is needed before a conclusion can be drawn for this issue.

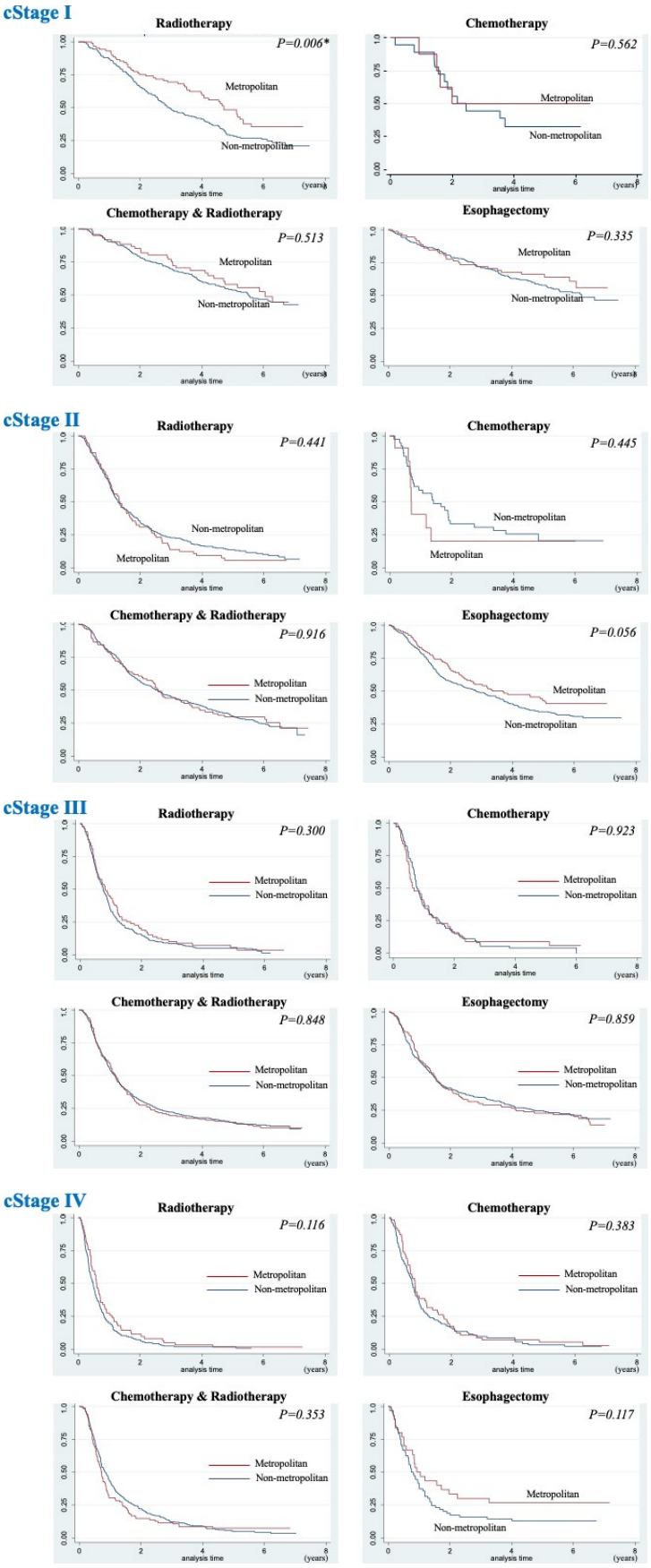

FIGURE 2 Overall survival among patients aged 75 y or more with cStage I-IV thoracic esophageal cancer divided based on treatment method (radiotherapy alone, chemotherapy alone, chemoradiotherapy, esophagectomy with or without adjuvant therapy) in metropolitan and nonmetropolitan areas. The asterisk indicates there is a significant difference between cStage I patients treated with radiotherapy alone in the two areas

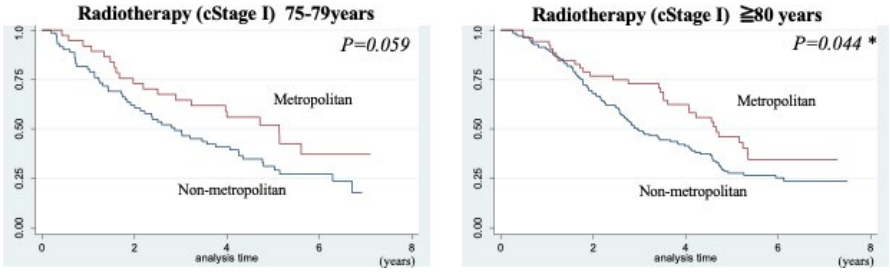

FIGURE 3 The overall survival among patients aged 75-79 y and 80 y or more with cStage I thoracic esophageal cancer treated with radiotherapy alone in metropolitan and nonmetropolitan areas. The asterisk indicates there is a significant difference in patients aged 80 y or more between two areas

TABLE 4 Multivariable Cox proportional hazard analysis for treatment area (metropolitan or nonmetropolitan) to survival (cStage I-IV, n = 4924)

	Model 1			Model 2		
	HR	95%CI	*P*	HR	95%CI	*P*
cStage I Ref: Provincial areas						
Metropolitan areas (overall)	0.76	0.61-0.94	.011			
Metropolitan areas (radiation alone)				0.68	0.49-0.94	.020
Metropolitan areas (chemotherapy alone)				0.73	0.24-2.27	.588
Metropolitan areas (radiation and chemotherapy)				.92	0.61-1.39	.692
Metropolitan areas (esophagectomy)				0.88	0.57-1.34	.541
cStage II Ref: Provincial areas						
Metropolitan areas (overall)	0.99	0.84-1.15	.862			
Metropolitan areas (radiation alone)				1.13	0.86-1.50	.378
Metropolitan areas (chemotherapy alone)				1.42	0.65-3.11	.379
Metropolitan areas (radiation and chemotherapy)				1.05	0.81-1.37	.702
Metropolitan areas (esophagectomy)				0.81	0.62-1.05	.114
cStage III Ref: Provincial areas						
Metropolitan areas (overall)	0.99	0.87-1.13	.904			
Metropolitan areas (radiation alone)				0.84	0.64-1.10	.200
Metropolitan areas (chemotherapy alone)				0.97	0.66-1.42	.859
Metropolitan areas (radiation and chemotherapy)				1.02	0.84-1.25	.821
Metropolitan areas (esophagectomy)				1.08	0.86-1.37	.513
cStage IV Ref: Provincial areas						
Metropolitan areas (overall)	0.91	0.77-1.06	.223			
Metropolitan areas (radiation alone)				0.79	0.59-1.07	.130
Metropolitan areas (chemotherapy alone)				0.83	0.60-1.15	.269
Metropolitan areas (radiation and chemotherapy)				1.19	0.94-1.51	.145
Metropolitan areas (esophagectomy)				0.62	0.38-1.02	.059

Note: Model 1 includes interaction terms between treatment areas and cStage after adjusting the analysis stratified based on age, sex, and first-line treatments.

Model 2 includes interaction terms between treatment areas, cStage, and the first-line treatments after adjusting the analysis stratified based on age and sex.

In addition, although thoracoscopic esophagectomy was performed in 20% of patients in both groups, the 3-year survival rate was 58.0% (51.0%-64.4%) in nonmetropolitan areas and 63.7% (51.4%-73.6%) in metropolitan areas ($P = .042$). This likely reflects the higher number of surgical cases per facility in metropolitan areas as well as greater familiarity with thoracoscopic esophagectomy and fewer surgery-related complications and deaths.

Our study has several limitations. First, the cancer data were collected only from designated cancer care hospitals and only for first-course treatments provided by the registering facility. Second, the division between metropolitan and nonmetropolitan areas is prefectural and rough. It may be necessary to divide by municipality for more precise analyses, but we do not have those data in this study, and it is common to receive cancer treatments at hospitals across municipalities. Third, our data do not include information on comorbidity or performance status, which is a serious limitation of this study. Fourth, staging accuracy may vary among institutions using cStage. In fact, cN- and cM-positive patients were more common in metropolitan areas than in nonmetropolitan areas. It is unclear whether this is due to a difference in ability to make a clinical diagnosis or delay in early diagnosis, but it is an inherent weakness of all studies using cancer registration databases.

In conclusion, there are differences in treatment strategy and survival outcomes among elderly patients with cStage I thoracic esophageal cancer between metropolitan and nonmetropolitan areas. In metropolitan areas with extensive urban services and medical delivery systems, it is possible that appropriate treatment was given after a thorough assessment of the risks to the elderly. On the other hand, background information such as comorbidity and performance status may have more strongly influenced prognosis and treatment decisions.

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ORCID

Satoru Motoyama https://orcid.org/0000-0001-9191-2563

REFERENCES

1. Kitagawa Y, Uno T, Oyama T, et al. Esophageal cancer practice guidelines 2017 edited by the Japan Esophageal Society: part 1. *Esophagus*. 2019;16:1-24.
2. Kitagawa Y, Uno T, Oyama T, et al. Esophageal cancer practice guidelines 2017 edited by the Japan esophageal society: part 2. *Esophagus*. 2019;16:25-43.
3. Motoyama S, Maeda E, Iijima K, et al. Does esophagectomy provide a survival advantage to patients aged 80 Years or Older? Analyzing 5,066 patients in the national database of Hospital-based cancer registries in Japan. *Ann Surg*. 2020. https://doi.org/10.1097/SLA.0000000000004437. Online ahead of print.
4. Finlayson E, Fan Z, Birkmeyer JD. Outcomes in octogenarians undergoing high-risk cancer operation: a national study. *J Am Coll Surg*. 2007;205:729-734.
5. Makary MA, Segev DL, Pronovost PJ, et al. Frailty as a predictor of surgical outcomes in older patients. *J Am Coll Surg*. 2010;210:901-908.
6. Higashi T, Nakamura F, Shibata A, Emori Y, Nishimoto H. The national database of Hospital-based Cancer Registries: a nationwide infrastructure to support evidence-based cancer care and cancer control policy in Japan. *Jpn J Clin Oncol*. 2014;44:2-8.
7. Wildiers H, Heeren P, Puts M, et al. International society of geriatric oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol*. 2014;32:2595603.
8. Jingu K, Numasaki H, Toh Y, et al. Chemoradiotherapy and radiotherapy alone in patients with esophageal cancer aged 80 years or older based on the comprehensive registry of esophageal cancer in Japan. *Esophagus*. 2020;17:223-229.
9. Semenkovich TR, Hudson JL, Subramanian M, et al. Trends in treatment of T1N0 esophageal cancer. *Ann Surg*. 2019;270:434-443.
10. Numasaki H, Teshima T, Nishimura T, et al. Japanese structure survey of radiation oncology in 2011. *J Radiat Res*. 2019;60:786-802.
11. Jingu K, Takahashi N, Murakami Y, et al. Is concurrent chemotherapy with radiotherapy for esophageal cancer beneficial in patients aged 80 years or older? *Anticancer Res*. 2019;39:4279-4281.
12. Motoyama S, Maeda E, Yano M, et al. Appropriateness of the institute certification system for esophageal surgeries by the Japan Esophageal Society: evaluation of survival outcomes using data from the National Database of Hospital-Based Cancer Registries in Japan. *Esophagus*. 2019;16:114-121.
13. Motoyama S, Yamamoto H, Miyata H, et al. Impact of certification status of the institute and surgeon on short-term outcomes after surgery for thoracic esophageal cancer: evaluation using data on 16,752 patients from the National Clinical Database in Japan. *Esophagus*. 2020;17:41-49.
14. Motoyama S, Maeda E, Yano M, et al. Esophagectomy performed at institutes certified by the Japan Esophageal Society provide long-term survival advantages to esophageal cancer patients: second report analyzing 4897 cases with propensity score matching. *Esophagus*. 2020;17:141-148.
15. Nishigori T, Miyata H, Okabe H, et al. Impact of hospital volume on risk-adjusted mortality following oesophagectomy in Japan. *Br J Surg*. 2016;103:1880-1886.
16. Markar SR, Mackenzie H, Askari A, Faiz O, Hanna GB. Effect of esophageal cancer surgeon volume on management and mortality from emergency upper gastrointestinal conditions: population-based cohort study. *Ann Surg*. 2017;266:847-853.
17. Andrew C, Chang MD. Centralizing Esophagectomy to improve outcomes and enhance clinical research. *Ann Thrac Surg*. 2018;106:916-923.

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