

Original Article

Impact of the coronavirus disease 2019 pandemic on first-visit patients with oesophageal cancer in the first infection wave in Saitama prefecture near Tokyo: a single-centre retrospective study

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Abstract

Background: Although the novel coronavirus disease 2019 did not lead to a serious medical collapse in Japan, its impact on treatment of oesophageal cancer has rarely been investigated. This study aimed to investigate the influence of the pandemic on consultation status and initial treatment in patients with primary oesophageal cancer.

Methods: A retrospective study was conducted among 546 patients with oesophageal cancer who visited our hospital from April 2018 to March 2021. Pre-pandemic and pandemic data were compared with the clinical features, oncological factors and initial treatment as outcome measures.

Results: Diagnoses of oesophageal cancer decreased during the early phase of the pandemic from April to June ($P = 0.048$); however, there was no significant difference between the pre-pandemic and pandemic periods throughout the year. The proportion of patients diagnosed with distant metastases significantly increased during the pandemic ($P = 0.026$), while the proportion of those who underwent initial radical treatment decreased ($P = 0.044$). The rate of definitive chemoradiotherapy decreased by 58.6% relative to pre-pandemic levels ($P = 0.001$).

Conclusions: Patients may have refrained from consultation during the early phase of the coronavirus disease 2019 pandemic. The resultant delay in diagnosis may have led to an increase in the number of patients who were not indicated for radical treatment, as well as a decrease in the number of those who underwent definitive chemoradiotherapy. Our findings highlight the need to maintain the health care system and raise awareness on the importance of consultation.

Key words: COVID-19, oesophageal neoplasms, Japan, referral and consultation, chemoradiotherapy

Introduction

The first case of novel coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China in December 2019, following which it quickly spread worldwide, leading to a serious pandemic. The COVID-19 pandemic continues to significantly affect global health care systems, and serious infections have placed substantial pressure on medical resources and have negatively affected the treatment of other diseases.

Regarding cancer, screening has been suspended, routine diagnostic work has been deferred and only urgent symptomatic cases are prioritized for diagnostic intervention. Substantial increases in the number of avoidable cancer deaths are expected given the diagnostic delays caused by the COVID-19 pandemic (1). Accordingly, a study of gastrointestinal cancer conducted in the UK revealed decreases in endoscopic activity and diagnoses of cancer, including pancreaticobiliary, oesophageal, gastric and colorectal cancers (2).

In Japan, the first case of COVID-19 was reported on 15 January 2020, and the first state of emergency was declared in seven prefectures (including Saitama Prefecture, where our hospital is located) on 7 April 2020. Although no serious medical collapse has occurred, several waves of infection have been confirmed as of April 2021. Among the lifestyle changes that have occurred during the COVID-19 pandemic are behavioural changes, such as refraining from visiting a medical institution. A recent cross-sectional study in the USA revealed that weekly diagnoses during the pandemic have decreased for six cancers, including breast, colorectal, lung, pancreatic, gastric and oesophageal cancers (3). A single-centre study in the UK reported a reduction in the number of patients referred for oesophageal cancer during the pandemic compared with the same period in 2019 (4). In Japan, a recent study on the status of oesophageal cancer consultations revealed no significant differences; however, the number of patients with stage 0 to II disease decreased, whereas that of patients with stage III or IV disease increased (5).

To date, few studies have investigated the deleterious impact of the COVID-19 pandemic on the treatment of oesophageal cancer. In addition, the scale of the pandemic varies greatly among countries and regions, highlighting the need for further studies in Japan. We aimed to conduct a comparative study of the consultation status and initial treatment of patients with primary oesophageal cancer who visited our institution before and during the COVID-19 pandemic.

Materials and methods

Study design and patients

This retrospective study included 546 patients with new oesophageal cancer who first visited our hospital from April 2018 to March 2021. The 1-year period from April 2020 to March 2021 during the COVID-19 pandemic was compared with the 2-year period from April 2018 to March 2020 before the pandemic. In addition, patient background characteristics were compared between the 2 years before the COVID-19 pandemic, and the presence or absence of differences between the two periods was verified. The target oesophageal cancers were cervical and thoracic oesophageal cancers, whereas cancers with the main lesion in the pharynx or oesophagogastric junction were excluded. None of the patients with oesophageal cancer had a history of COVID-19 infection during the period under consideration.

The study was approved by the Institutional Review Board of the Saitama Medical University International Medical Center (approval number 2021-114). All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1964

Declaration of Helsinki and its later versions. The requirement for informed consent was waived owing to the retrospective nature of the study.

Institution

Our hospital is a core institution for oesophageal cancer treatment in the secondary medical area where the hospital is located and in the adjacent secondary medical area. In 2017, the share of medical care for patients with oesophageal cancer in the secondary care area exceeded 70%, and the number of first-visit patients did not decrease between 2017 and 2019. In the early days of the pandemic, a dedicated department was set up to manage COVID-19 patients. During the observation period of the COVID-19 pandemic, no medical restrictions were imposed at our institution.

Data collection and outcome measures

Medical records were used to obtain data regarding the total number of patients; age; sex; American Society of Anesthesiologists physical status (ASA-PS) (6); chief complaints; the period from symptom awareness to consultation; measures of nutritional status, such as the controlling nutritional status (CONUT) score and prognostic nutrition index (PNI) (7, 8); tumour location, histology; clinical stage; and initial treatment strategies.

Clinical diagnosis and treatment

Clinical diagnosis was performed comprehensively with reference to esophagogastroduodenoscopy and cervico-thoracoabdominal computed tomography, as well as upper gastrointestinal series and positron emission tomography-computed tomography when necessary. Tumour staging was performed based on the eighth edition of the International Union Against Cancer guidelines (AJCC/UICC-TNM) and Japanese Classification of Esophageal Cancer, 11th edition (JES-TNM) (9, 10). The treatment policy for each patient was determined by the cancer board, which included radiologists, medical oncologists and surgeons, based on the Esophageal Cancer Practice Guidelines 2017, edited by the Japan Esophageal Society (11). Endoscopic resection where curative resection is expected according to the Esophageal Cancer Practice Guidelines 2017 and radical esophagectomy with regional lymph node dissection and definitive chemoradiotherapy (dCRT), which covers all of the target lesions with prophylactic irradiation of ≥ 50 Gy, were considered radical initial treatments. Therefore, locally controlled chemoradiotherapy for patients with distant metastases corresponding to systemic metastases was considered as palliative treatment. All other initial treatments were considered palliative treatments.

Statistical analysis

Groups were compared using the χ^2 test or Fisher's exact test for categorical variables and the Mann-Whitney U-test for continuous variables, as appropriate. Differences were considered statistically significant at two-tailed $P < 0.05$. All statistical analyses were performed using the SPSS software (version 24.0; IBM Corp., Armonk, NY, USA).

Results

Comparison between the first- and second-halves of the pre-pandemic period

The numbers and characteristics of first-visit patients were compared between April 2018 to March 2019 (first half) and April 2019 to March 2020 (second half). The results are shown in Table 1.

Table 1. Patient characteristics and initial treatments for the first and second halves of the pre-pandemic period and during the COVID-19 pandemic

Factor	Pre-pandemic period		P	Pre-pandemic period	Pandemic period	P
	First half	Second half				
Total number of patients	184	194		378	168	
Number of first-visit patients by month, median (range)	14.5 (10–25)	17 (11–20)	0.443	15.5 (10–25)	14.5 (6–19)	0.265
ASA-PS			0.149			0.750
0–2	163 (88.6)	181 (93.3)		344 (91.0)	151 (89.9)	
3–4	21 (11.4)	13 (6.7)		34 (9.0)	17 (10.1)	
Sex			0.549			0.294
Male	157 (85.3)	170 (87.6)		327 (86.5)	139 (82.7)	
Female	27 (14.7)	24 (12.4)		51 (13.5)	29 (17.3)	
Age, years, median (range)	71 (39–86)	72 (38–90)	0.237	72 (38–90)	72 (49–87)	0.987
Complaints at the first medical consultation			0.212			0.511
Absence	72 (39.1)	89 (45.9)		161 (42.6)	66 (39.3)	
Presence	112 (60.9)	105 (54.1)		217 (57.4)	102 (60.7)	
Period with symptoms, months, median (range)	2 (0–25)	2 (0–80)	0.793	2 (0–80)	3 (0–42)	0.988
CONUT, median (range)	1 (0–11)	1 (0–9)	0.748	1 (0–11)	1 (0–12)	0.418
PNI, median (range)	47.2 (23.7–65.2)	46.8 (30.5–58.5)	0.596	46.9 (23.7–65.2)	47.7 (21.9–62.5)	0.319
Histology			0.641			0.087
SCC	176 (95.7)	183 (94.3)		359 (95.0)	153 (91.1)	
non-SCC	8 (4.3)	11 (5.7)		19 (5.0)	15 (8.9)	
Tumour location			0.137			0.002*
Ce	15 (8.2)	11 (5.7)		26 (6.9)	4 (2.4)	
Ut	23 (12.5)	17 (8.7)		40 (10.6)	20 (11.9)	
Mt	100 (54.3)	98 (50.5)		198 (50.3)	69 (41.1)	
Lt	46 (25.0)	68 (35.1)		114 (30.2)	75 (44.6)	
Clinical tumour depth			0.100			0.601
cT1	65	81		146 (38.6)	67 (39.9)	
cT2–3	76	84		160 (42.3)	75 (44.6)	
cT4	43	29		72 (19.0)	26 (15.5)	
Clinical lymph node metastasis			0.681			0.308
Absence	90	100		190 (50.3)	76 (45.2)	
Presence	94	94		188 (49.7)	92 (54.8)	
Clinical distant metastasis			0.504			0.026*
Absence	167	171		338 (89.4)	138 (82.1)	
Presence	17	23		40 (10.6)	30 (17.9)	
AJCC/UICC-cStage			0.548			0.402
0–I	65 (35.3)	80 (41.2)		145 (38.4)	66 (39.3)	
II–III	57 (31.0)	58 (29.9)		115 (30.4)	43 (25.6)	
IVA	34 (18.5)	27 (13.9)		61 (16.1)	25 (14.9)	
IVB	28 (15.2)	29 (14.9)		57 (15.1)	34 (20.2)	
JES-cStage			0.346			0.077
0–I	65 (35.3)	74 (38.1)		139 (36.8)	64 (38.1)	
II–III	71 (38.6)	76 (39.2)		147 (38.9)	57 (33.9)	
IVa	31 (16.8)	21 (10.8)		52 (13.8)	17 (10.1)	
IVb	17 (9.2)	23 (11.9)		40 (10.6)	30 (17.9)	
Initial treatment			0.731			0.044*
Radical treatment	135 (73.4)	139 (71.6)		274 (72.5)	107 (63.7)	
Palliative treatment	49 (26.6)	55 (28.4)		104 (27.5)	61 (36.3)	

Abbreviations; ASA-PS, American Society of Anesthesiologists physical status; CONUT, controlling nutritional status; PNI, prognostic nutrition index; AJCC/UICC, American Joint Committee on Cancer/International Union Against Can; cStage, clinical stage; JES, Japan Esophageal Society; SCC, squamous cell carcinoma; Ce, cervical oesophagus; Ut, upper thoracic oesophagus; Mt, middle thoracic oesophagus; Lt, lower thoracic oesophagus; OR, odds ratio; CI, confidence interval.

* $P < 0.05$.

There were no significant differences in the number of first-visit patients each month, the presence or absence of symptoms at the first visit, the symptomatic period, age, sex, nutritional indices, tumour factors such as clinical stage or initial treatment between the two periods.

Comparison before and during the COVID-19 pandemic

Diagnoses of cervical and middle thoracic lesions during the COVID-19 pandemic decreased relative to those prior to the pandemic, whereas those of lower thoracic lesions increased ($P = 0.002$) (Table 1). The proportion of patients with distant metastasis increased from 10.6 to 17.9%, and that of those who underwent initial radical treatment decreased from 72.5 to 63.7% during the pandemic ($P = 0.026$ and 0.044, respectively). However, there were no significant differences in the other factors, including the number of patients at the first visit, the clinical situation at the first visit and AJCC/UICC- or JES-clinical stage, between the two periods.

Number of first-visit patients per month

The numbers of first-visit patients in each month during the 3-year study period are shown in Fig. 1. Although no significant difference was observed between the pre-pandemic and pandemic periods throughout the year (mean \pm standard deviation [SD]; 15.8 ± 0.8 vs. 14.0 ± 1.1 , $P = 0.265$), the number of patients decreased during the early phase of the pandemic from April to June (16.0 ± 1.2 vs 9.7 ± 2.0 , $P = 0.048$). On the other hand, from July to March, the number of patients did not significantly change before and after the pandemic (15.7 ± 1.0 vs 15.4 ± 0.9 , $P = 0.940$).

Frequency of radical treatment by clinical stage according to AJCC/UICC and JES clinical stage

The proportion of patients who underwent radical treatment at the AJCC/UICC-cStage IVB was significantly reduced from 19.3 to 2.9% during the COVID-19 pandemic ($P = 0.028$), whereas no significant difference in the rate of radical treatment was observed for patients with other AJCC/UICC-cStages between the pre-pandemic and pandemic periods. On the other hand, the proportion of patients who underwent radical treatment at JES-cStage IVa was significantly reduced from 71.2 to 41.2% ($P = 0.041$), whereas no significant difference in the rate of radical treatment was observed for patients with other JES-cStages between the pre-pandemic and pandemic periods (Fig. 2).

Proportion and number of patients receiving each initial treatment

Regarding initial treatment strategies, dCRT decreased from 18.5 to 8.3% during the pandemic (Table 2). However, there was no change in the proportion of patients who underwent endoscopic resection or radical surgery with or without neoadjuvant chemotherapy. The rate of dCRT decreased by 58.6% ($P = 0.001$). The numbers of patients undergoing endoscopic treatment, surgery with or without neoadjuvant chemotherapy, and palliative treatment were all reduced; however, the differences were not significant (Fig. 3).

Comparison of JES-cStage IVa between before and during the COVID-19 pandemic

The subgroup analysis results on JES-cStage IVa, which is typically indicated for dCRT and corresponds to unresectable locally

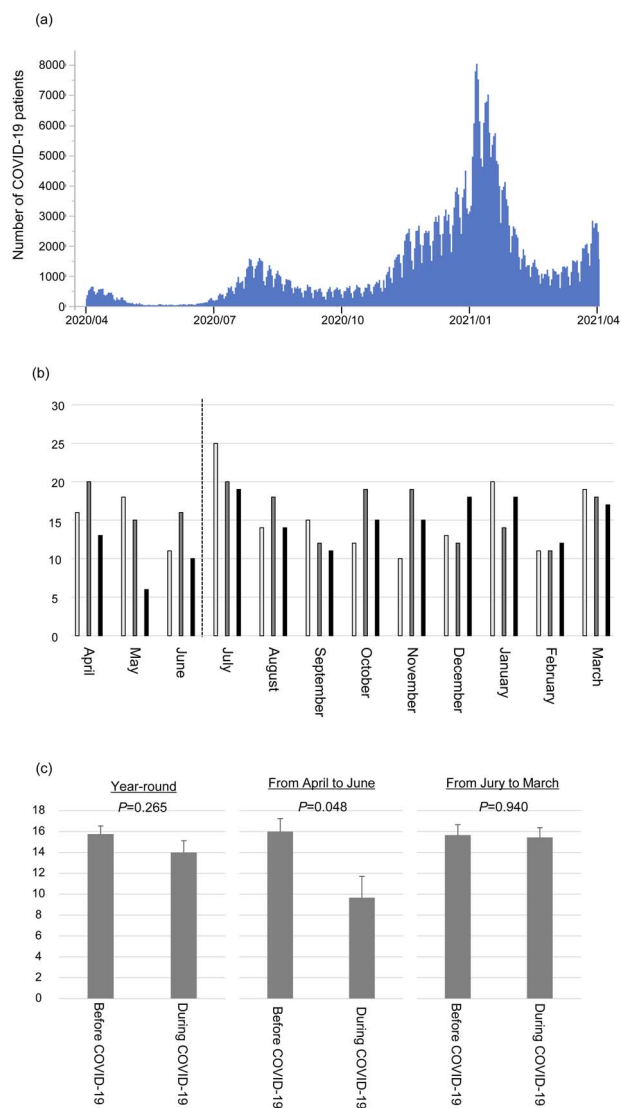


Figure 1. Number of first-visit patients per month. (a) Changes in the number of patients with novel coronavirus disease 2019 (COVID-19) in Japan from April 2020 to March 2021. (b) Changes in each month over the 3-year study period. The white, grey and black bars indicate the number of patients from April 2018 to March 2019, April 2019 to March 2020 and April 2020 to March 2021, respectively. The dotted line between June and July marks the boundary of the early phase. (c) Comparison of the number of first-visit patients for the full year, from April to June, and from July to March of the following year between the pre-pandemic and pandemic periods.

advanced oesophageal cancer, are shown in Table 3. There were no significant differences in the characteristics at the first visit and the selection of initial treatment between the two periods. The proportion of patients with poor PS increased from 15.4 to 47.1% before and during the COVID-19 pandemic, respectively, and the diagnoses of upper and middle thoracic lesions both increased ($P = 0.017$ and 0.002, respectively). Moreover, the proportion of patients who underwent radical treatment decreased from 71.2 to 41.2% ($P = 0.041$).

Comparison of JES-cStage IVb before and during the COVID-19 pandemic

The results of the JES-cStage IVb subgroup analysis, in whom radical treatment is not indicated because of the presence of distant

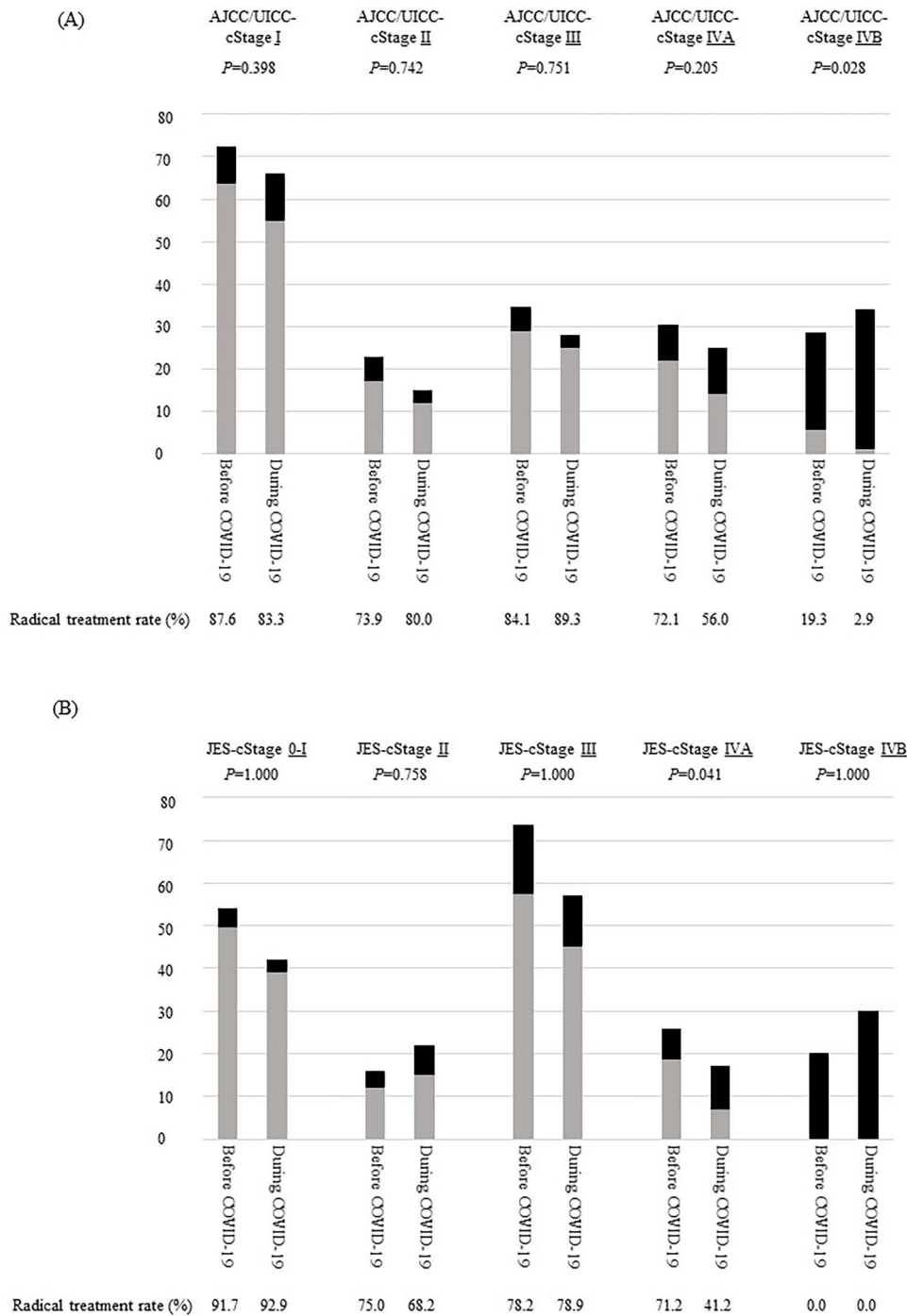


Figure 2. Comparison of radical treatment rates at each clinical stage. (a) According to the American Joint Committee on Cancer/International Union Against Cancer classification before and during the COVID-19 pandemic. (b) According to the Japanese Classification of Esophageal Cancer classification before and during the COVID-19 pandemic. The vertical axis shows the number of patients per year, pre- and during the pandemic. The number of patients who received palliative management as the initial treatment is shown by the black bar, and the number of patients who underwent radical treatment is shown by the grey bar.

metastases, are shown in [Table 4](#). The number of patients per year increased from 20 to 30. Although there were no significant differences in patient characteristics at the first visit between the two periods, the proportion with poor PS decreased from 32.5 to 16.7%, and the symptomatic period lengthened from 4.5 to 6.5 months before and during the COVID-19 pandemic, respectively ($P = 0.134$

and 0.105, respectively). The proportion of patients who chose best supportive care (BSC) without palliative systemic chemotherapy decreased significantly from 65.0% before the pandemic to 26.7% afterwards ($P = 0.002$). No difference was observed in clinical metastatic sites between the two periods ([Supplementary Table 1](#)).

Table 2. Initial treatments for the first and second halves of the pre-pandemic period and during the COVID-19 pandemic

Factor	Pre-pandemic period				<i>P</i>	Pre-pandemic period	Pandemic period	<i>P</i>	
	First half		Second half						
Total number of patients	184		194			378	168		
Initial treatment					0.320			0.010*	
Endoscopic resection	42	(22.8)	57	(29.4)		99	(26.2)	41	(24.4)
Radical oesophagectomy ± Neoadjuvant chemotherapy	58	(31.5)	47	(24.2)		105	(27.8)	52	(31.0)
Definitive chemoradiotherapy	35	(19.0)	35	(18.0)		70	(18.5)	14	(8.3)
BSC or palliative treatment	49	(26.6)	55	(28.4)		104	(27.5)	61	(36.3)

Abbreviations: BSC, best supportive care; OR, odds ratio; CI, confidence interval. **P* < 0.05.

Table 3. Comparison of characteristics and initial treatments of patients with JES-Stage IVa between the first and second half of the period before the COVID-19 pandemic and between before and during the COVID-19 pandemic

Factor	Pre-pandemic period				<i>P</i>	Pre-pandemic period	Pandemic period	<i>P</i>		
	First half		Second half							
Total number of patients	31		21			52	17			
ASA-PS					0.449			0.017*		
0–2	25	(80.6)	19	(90.5)		44	(84.6)	9	(52.9)	
3–4	6	(19.4)	2	(9.5)		8	(15.4)	8	(47.1)	
Sex					0.675			0.248		
Male	28	(90.3)	18	(85.7)		46	(88.5)	13	(76.5)	
Female	3	(9.7)	3	(14.3)		6	(11.5)	4	(23.5)	
Age, years, median (range)	72 (39–86)		70 (54–85)		0.866	70.5 (39–86)		73 (51–84)		0.244
Complaints at the first medical consultation					0.558					0.590
Absence	1	(3.2)	2	(9.5)		3	(5.8)	2	(11.8)	
Presence	30	(96.8)	19	(90.5)		49	(94.2)	15	(88.2)	
Period with symptoms, months, median (range)	6 (0–25)		4 (0–30)		0.873	4.5 (0–30)		4 (0–24)		0.307
CONUT, median (range)	2 (0–11)		2 (0–7)		0.399	2 (0–11)		2 (0–5)		0.895
PNI, median (range)	43.7 (23.7–53.5)		46.1 (35.9–57.3)		0.569	45.4 (23.7–57.3)		45.4 (35.3–54.7)		0.994
Histology					1.000					1.000
SCC	31	(100.0)	21	(100.0)		52	(100.0)	17	(100.0)	
Non-SCC	0	(0.0)	0	(0.0)		0	(0.0)	0	(0.0)	
Tumour location					0.182					0.002*
Ce	8	(25.8)	2	(9.5)		10	(19.2)	3	(1.8)	
Ut	7	(22.6)	6	(28.5)		13	(25.0)	10	(58.8)	
Mt	16	(51.6)	11	(52.4)		27	(51.9)	1	(5.9)	
Lt	0	(0.0)	2	(9.5)		2	(3.8)	3	(17.6)	
Initial treatment					0.551					0.041*
Radical treatment	21	(67.7)	16	(76.2)		37	(71.2)	7	(41.2)	
Palliative treatment	10	(32.3)	5	(23.8)		15	(28.8)	10	(58.8)	

Abbreviations: JES, Japanese Classification of Esophageal Cancer **P* < 0.05.

Radical surgery

There were no significant differences in the characteristics of first-visit patients between the first and second halves of the pre-pandemic period (Table 5). In terms of tumour location, diagnoses of middle thoracic lesions decreased, whereas those of lower thoracic lesions increased between the pre-pandemic and pandemic periods. No significant differences in other factors, including the clinical situation at the first visit, AJCC/UICC-stage, JES-stage and the presence or

absence of neoadjuvant chemotherapy, were observed between the two periods.

Discussion

In this study, we compared the consultation status and the initial treatment of patients with primary oesophageal cancer who visited our institution before and after the COVID-19 pandemic. Here, we

Table 4. Comparison of characteristics and initial treatments among patients with JES-Stage IVb during the first and second half of the period before the COVID-19 pandemic, and before and during the pandemic

Factor	Before COVID-19		P value	Before COVID-19		During COVID-19		P value
	The first half	The second half						
Total number of patients	17	23		40	30			
ASA-PS			1.000					0.134
0–2	12 (70.6%)	15 (65.2%)		27 (67.5%)	25 (83.3%)			
3–4	5 (29.4%)	8 (34.8%)		13 (32.5%)	5 (16.7%)			
Sex			1.000					1.000
Male	16 (94.1%)	21 (91.3%)		37 (92.5%)	27 (90.0%)			
Female	1 (5.9%)	2 (8.7%)		3 (7.5%)	3 (10.0%)			
Age (median; range)	69 (62–81)	76 (41–88)	0.156	72 (41–88)	72 (54–82)			0.429
Complaint at the first medical consultation			0.565					1.000
Absence	2 (11.8%)	1 (4.3%)		3 (7.5%)	3 (10.0%)			
Presence	15 (88.2%)	22 (95.7%)		37 (92.5%)	27 (90.0%)			
Period with symptoms (month, median; range)	4 (0–10)	6 (0–14)	0.371	4.5 (0–14)	6.5 (0–40)			0.105
Histology			1.000					0.066
SCC	16 (94.1%)	22 (95.7%)		38 (95.0%)	24 (80.0%)			
Non-SCC	1 (5.9%)	1 (4.3%)		2 (5.0%)	6 (20.0%)			
Tumour location			0.374					0.969
Ce	1 (5.9%)	1 (4.3%)		2 (5.0%)	1 (3.3%)			
Ut	2 (11.8%)	1 (4.3%)		3 (7.5%)	3 (10.0%)			
Mt	9 (52.9%)	8 (34.8%)		17 (42.5%)	13 (43.3%)			
Lt	5 (29.4%)	13 (56.5%)		18 (45.0%)	13 (43.4%)			
Clinical tumour depth			0.667					0.506
cT1	0 (38.6%)	1 (4.3%)		1 (2.5%)	1 (3.3%)			
cT2–3	11 (42.3%)	15 (65.2%)		26 (65.0%)	23 (76.7%)			
cT4	6 (19.0%)	7 (30.4%)		13 (32.5%)	6 (20.0%)			
Clinical lymph node metastasis			0.499					0.503
Absent	0 (0.0%)	2 (8.7%)		2 (5.0%)	0 (0.0%)			
Present	17 (100.0%)	21 (91.3%)		38 (95.0%)	30 (100.0%)			
Initial treatment			0.739					0.002*
Systemic chemotherapy (± radiotherapy)	5 (29.4%)	9 (39.1%)		14 (35.0%)	22 (73.3%)			
BSC (± radiotherapy)	12 (70.6%)	14 (60.9%)		26 (65.0%)	8 (26.7%)			

Abbreviations; JES: Japanese Classification of Esophageal Cancer, * $P < 0.05$.

discuss our four main findings. First, we observed no change in the number of first-visit patients throughout the year, although a decrease during the early phase (April to June) of the pandemic was noted. On the other hand, to date, four infection waves have been confirmed since April 2020, as Fig. 1a shows. Thus, there was a significant difference between the change in the number of first-visit patients in our study and the change in the number of COVID-19 patients during the pandemic in Japan. In addition to the fact that many hospitals temporarily stopped performing endoscopies for medical examination in the early phase of the pandemic based on the recommendation of the Japan Gastroenterological Endoscopy Society (12), behavioural changes that caused patients to refrain from consultations may have been significant in the early phase. However, despite the fact that three major infection waves were confirmed in the period from June 2020 to April 2021, the number of first-visit patients during this period has recovered to almost the same level as that in pre-pandemic. This may be due to multiple factors, but along with the medical provider's factor of resuming diagnostic endoscopy, the behavioural change of patients refraining

from consultations, which was remarkable in the early phase of the pandemic, has returned to the pre-pandemic level. It seems that the behavioural changes themselves might continue to vary over time with the prolongation of the pandemic. Second, the number of patients who underwent radical treatment decreased during the pandemic. Although the changes in clinical stage according to the AJCC/UICC classification were unclear, the proportion of patients with clinical distant metastases according to the JES classification increased during the pandemic, suggesting that there were delays in diagnosis and radical treatment. Third, no changes in the frequency of endoscopic treatment or surgery were noted, although there was a decrease in the number of patients who underwent dCRT. Fourth, among patients with distant metastases, in whom radical treatment is not indicated, the proportion who underwent palliative systemic chemotherapy instead of BSC was increasing.

The decision-making process for initial treatment in patients with oesophageal cancer requires consideration of patient factors, such as PS, major organ functions and cognitive functions, in addition to clinical staging. In general, the administration of invasive

Table 5. Comparison of characteristics of patients who underwent radical esophagectomy between the first and second half of the period before the COVID-19 pandemic and between before and during the COVID-19 pandemic

Factor	Pre-pandemic period		P value	Pre-pandemic period	Pandemic period	P value
	The first half	The second half				
Total number of patients	58	47		105	52	
Sex			0.751			0.438
Male	51 (87.9)	43 (91.4)		94 (89.5)	44 (84.6)	
Female	7 (12.1)	4 (8.5)		11 (10.5)	8 (15.4)	
Age, years, median (range)	69 (39–86)	70 (51–83)	0.943	70 (38–86)	71 (49–86)	0.279
Complaints at the first medical consultation						
Absence	16 (27.6)	13 (27.7)		29 (27.6)	11 (21.2)	
Presence	42 (72.4)	34 (72.3)	1.000	76 (72.4)	41 (78.8)	0.440
	4.5 (0–25)	6 (0–40)		0.473	5 (0–40)	
CONUT, median (range)	1 (0–6)	1 (0–6)	0.925	1 (0–6)	1 (0–9)	0.430
PNI, median (range)	48.8 (31.4–64.2)	48.3 (36.0–58.5)	0.645	48.6 (31.4–64.2)	48.9 (30.6–62.4)	0.804
Histology			0.536			0.601
SCC	53 (91.4)	41 (87.2)		94 (89.5)	45 (86.5)	
Non-SCC	5 (8.6)	6 (12.8)		11 (10.5)	7 (13.5)	
Tumour location			0.820			0.006*
Ce	2 (3.4)	1 (2.1)		3 (2.9)	0 (0.0)	
Ut	5 (8.6)	3 (8.74)		8 (7.6)	2 (3.8)	
Mt	30 (51.7)	22 (46.8)		52 (49.5)	14 (26.9)	
Lt	21 (36.2)	21 (44.7)		42 (40.0)	36 (69.2)	
Clinical tumour depth			0.174			0.857
cT1	14	5		19 (38.6)	11 (39.9)	
cT2–3	42	41		83 (42.3)	40 (44.6)	
cT4	2	1		3 (19.0)	1 (15.5)	
Clinical lymph node metastasis			0.237			0.126
Absence	30	18		48 (50.3)	17 (45.2)	
Presence	28	29		57 (49.7)	35 (54.8)	
Clinical distant metastasis			1.000			1.000
Absence	58	47		105 (89.4)	52 (82.1)	
Presence	0	0		0 (10.6)	0 (17.9)	
AJCC/UICC-cStage			0.426			0.420
I	14 (24.1)	5 (10.6)		19 (18.1)	11 (21.2)	
II	15 (25.9)	13 (27.7)		28 (26.7)	11 (21.2)	
III	25 (43.1)	23 (48.9)		48 (45.7)	23 (44.2)	
IVA	3 (5.2)	4 (8.5)		7 (6.7)	7 (13.5)	
IVB	1 (1.7)	2 (4.3)		3 (2.9)	0 (0.0)	
JES-cStage			0.090			0.693
0–I	14 (24.1)	4 (8.5)		18 (17.1)	10 (19.2)	
III	17 (29.3)	14 (29.8)		31 (29.5)	12 (23.1)	
III	27 (46.6)	29 (61.7)		56 (53.3)	30 (57.7)	
Neoadjuvant chemotherapy			0.140			0.214
Absence	22 (37.9)	11 (23.4)		33 (31.4)	22 (42.3)	
Presence	36 (62.1)	36 (76.6)		72 (68.6)	30 (57.7)	

Abbreviations: OR, odds ratio; CI: confidence interval. * $P < 0.05$.

treatment to patients with decreased PS or cognitive decline and standard chemotherapy to patients with renal failure is difficult. Moreover, recent studies have shown that nutritional indicators, such as CONUT and PNI, are predictors of short- and long-term outcomes in patients undergoing oesophageal cancer surgery (13–16). Delays in diagnosis during the COVID-19 pandemic may lead to decreases in the measures of nutritional status and PS due to disease progression. However, no such decreases were observed in our study, except for the subgroup of JES-cStage IVA. The human and physical resources of the medical provider may also influence treatment decisions made during the pandemic. A multicentre study

in Italy revealed an increase in waiting time before surgery and preoperative therapy due to a shortage of anesthesiologists and occupation of intensive care unit beds by intubated patients with COVID-19. Although the overall number of resections did not decrease compared with that in 2019, a higher rate of open oesophageal resections was observed (17). However, our institution did not implement any medical treatment restrictions during pandemic. Therefore, the observed decrease in the proportion of patients who underwent radical treatment during the COVID-19 pandemic was attributed to the progression of oesophageal cancer associated with the delay in diagnosis.

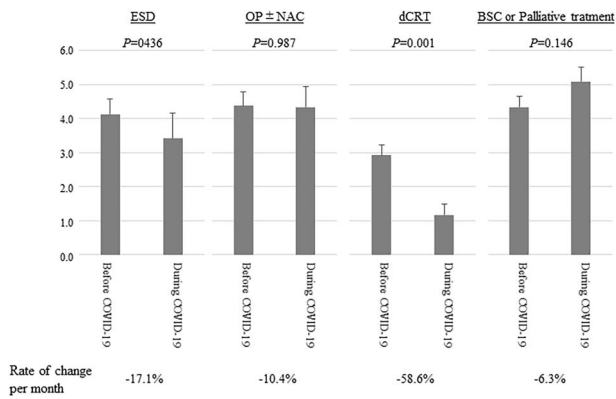


Figure 3. Comparison of the number of patients receiving each treatment per month before and during the COVID-19 pandemic. ESD, endoscopic submucosal dissection; OP, operation (radical esophagectomy); NAC, neoadjuvant chemotherapy; dCRT, definitive chemoradiotherapy; BSC, best supportive care.

However, there was no significant difference in the proportion of patients by AJCC/UICC-cStage. It seems to be inconsistent with the observed decrease in the proportion of patients who underwent radical treatment during the COVID-19 pandemic. The JES-TNM classification is based on the findings of several observational studies in Japan, which have suggested that prophylactic supraclavicular lymph node dissection contributes to increased postoperative survival, particularly in patients with thoracic mid-upper oesophageal cancer, and that its dissection has a relatively high efficacy index (18–21). Therefore, according to the JES-TNM classification, the supraclavicular lymph node corresponds to the regional lymph node, which corresponds to distant metastasis in the AJCC/UICC-TNM. Thus, in the treatment system in Japan, patients with AJCC/UICC-Stage IVb, who would normally be considered for palliative treatment, are mixed with those indicated for radical treatment. According to the JES-TNM classification, the indications for palliative treatment are limited to stage IVb. Therefore, the changes in the proportion of patients at each JES-cStage before and during the COVID-19 pandemic were consistent with the observed decrease in the proportion of patients who underwent radical treatment (i.e. an increase in the number of patients undergoing palliative treatment).

Surgery is the mainstay of radical treatment for resectable oesophageal cancer worldwide (11, 22). However, there are concerns that the medical strain caused by the pandemic will limit surgery and hospitalization. Studies in Western countries have highlighted the omission of some pretreatment examinations and treatment changes during the COVID-19 pandemic (4, 17). Moreover, prolonged surgery waiting time due to the COVID-19 pandemic has been suggested to decrease postoperative survival (23). Therefore, radiation therapy, which is less susceptible to the effects of COVID-19, is expected to complement surgical treatment (24).

However, we only found a significant decrease in the number of patients who underwent dCRT. In Japan, surgical resection is the standard treatment for resectable oesophageal cancer (11), and the negative impact of the COVID-19 pandemic on our health care system is limited. Therefore, dCRT may have been most affected by the decrease in the number of patients indicated for radical treatment. Moreover, in the subgroup analysis of JES-Stage IVa, an increase in proportion of patients with poor PS was observed. Although a phase III comparative study of induction chemotherapy followed by conversion surgery and dCRT for locally advanced

unresectable squamous cell carcinoma of the thoracic oesophageal is currently ongoing (25), dCRT is the current standard treatment for JES-Stage IVa in Japan. We speculate that this was one of the reasons for the increased frequency of avoiding dCRT and choosing palliative treatment. Although it is difficult to determine the extent to which the COVID-19 pandemic affected the increased proportion of patients with poor PS, refraining from consultation may have caused a decrease in the PS of patients with highly locally advanced oesophageal cancer at first visit.

On the other hand, in the subgroup analysis, the number of patients in the JES-Stage IVb subgroup, in whom radical treatment is not indicated due to the presence of distant metastases, increased during the pandemic, as did the proportion of patients who underwent palliative chemotherapy to prolong survival. Although no significant difference was observed, the subgroup analysis showed that the symptomatic period had increased by about 2 months while the proportion of patients with poor PS decreased. It was suggested that the delay in diagnosis of about 2 months due to patients refraining from consultation during the pandemic may have contributed to the progression of the disease to JES-Stage IVb. It can be observed that the decrease in PS during this period was limited.

We observed a change in the main location of oesophageal cancer. Because dysphagia may be less likely to occur in the cervical and upper thoracic oesophageal lesions due to swallowing pressure, refraining from consultation may have reduced the proportion of patients with cervical and upper thoracic oesophageal cancer. As the upper thoracic oesophagus is anatomically close to the trachea and aortic arch, tumour growth easily causes infiltration of important organs, resulting in a marked increase in the number of patients with upper thoracic oesophageal cancer as shown by the subgroup analysis results of JES-Stage IVa.

In Japan, a randomized controlled phase III trial is currently ongoing to prolong prognosis via more intensive chemotherapy in patients with metastatic or recurrent oesophageal cancer (26). Furthermore, although advances in palliative chemotherapy, such as the introduction of immune checkpoint inhibitors, are expected in the future, the prognosis of JES-Stage IVb, which is still not the target of curative treatment, is extremely poor. Refraining from consultation during the COVID-19 pandemic may have led to an increase in the number of patients with distant metastases and an increase in patients with poor PS and highly locally advanced cancer. The inability of patients with oesophageal cancer to undergo radical treatment is clearly a negative impact of the COVID-19 pandemic.

This study had some major limitations. First, this retrospective study used a single-centre, single-year design. As the scale of COVID-19 infection varies greatly depending on the region and time of the year, various biases may have occurred. However, the health care system of our institution has been maintained even during the pandemic, and the occupancy rate of patients receiving medical care for oesophageal cancer in the area is high. Therefore, we believe our results accurately reflect the impact of the COVID-19 pandemic on the treatment of oesophageal cancer in the region. Nonetheless, after the pandemic, large-scale nationwide studies are necessary. Second, as this study examined the patients with oesophageal cancer from the time of the first visit to the treatment decision, only a small portion of the effects of the COVID-19 pandemic has been clarified. Future studies should thus investigate the short- and long-term outcomes of each treatment in the context of COVID-19. Moreover, a detailed study of how the COVID-19 pandemic has impacted clinical oesophageal cancer treatment is desired. As the pandemic may have had an impact on social aspects, such as hospital visits or

drug procurement, clarifying its effects on the selection of systemic chemotherapy for palliative treatment is particularly pertinent.

In conclusion, our findings indicate that patients may have refrained from consultation in the early phase of the COVID-19 pandemic. Because of the delay in diagnosis, the number of patients in the non-adapted stage of radical treatment increased, and that of those who underwent dCRT decreased. In our hospital, where the medical system was maintained, no significant effects on endoscopic and surgical treatments was observed. Since the first wave, when the COVID-19 pandemic was relatively controlled in Japan compared with the situation in other countries, the delay in the diagnosis of oesophageal cancer and the accompanying disease progression were evident. Although fewer patients seem to have been refraining from consultation since the late phase, it is important to maintain the health care system and raise awareness on the importance of consultation until we gain control of the pandemic.

Supplementary Material

Supplementary material can be found at *Japanese Journal of Clinical Oncology* online.

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Conflict of interest

The authors declare no conflicts of interest.

Availability of data and materials

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

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