ORIGINAL

Clinical outcomes and prognostic factors of definitive radiotherapy for esophageal cancer

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Abstract : Purpose To assess the treatment results of definitive radiotherapy for esophageal cancer at Tokushima University Hospital and clarify the prognostic factors. Methods Seventy consecutive patients with esophageal cancer who underwent definitive radiotherapy between May 2004 and March 2012 were included in the present study. Local control rate, overall survival rate, and radiation morbidity were examined and univariate and multivariate analyses were performed to investigate prognostic factors. Results The 5-year overall survival rates of stages I, II, III, and IVA were 81%, 71%, 0%, and 9%, respectively. Performance status, clinical stage, and neoadjuvant chemotherapy were significant prognostic factors. A past history of interstitial pneumonia was associated with severe radiation-induced lung injury. Conclusions Patients who underwent definitive chemoradiotherapy for esophageal cancer in stage I/II showed good prognosis. However, treatment results of the patients in stage III/IV were not satisfactory, and those who could not undergo surgery after neoadjuvant chemotherapy had the worst prognosis. J. Med. Invest. 66 : 99-105, February, 2019

Keywords **:** *Clinical outcome, Chemoradiotherapy, Esophageal cancer, Radiotherapy, Neoadjuvant chemotherapy*

INTRODUCTION

Esophageal cancer is a disease that most commonly occurs in individuals in their 60s and 70s, and mainly in the middle thoracic esophagus. The most common pathological type in Japan is squamous cell carcinoma, which accounts for about 90% of cases (1). Comparisons between neoadjuvant chemotherapy followed by surgery (NAC-S) and definitive chemoradiotherapy in Japan (JCOG 1406-A) showed that overall survival was better in the NAC-S group and the reason for worse outcomes after chemoradiotherapy was considered to be late toxicity caused by radiotherapy and worse local control (2-4). However, good results of chemoradiotherapy followed by salvage esophagectomy have been reported in resectable esophageal cancer (5), and efficacy of definitive chemoradiotherapy has been reported even for stage IV which was considered an indication for palliative radiation therapy (6, 7). Therefore chemoradiotherapy has recently become the basic treatment for locally advanced esophageal cancer.

In Western countries 50.4 Gy is the standard dose based on results of a randomized controlled trial (8). However, in Japan radiotherapy of approximately 60 Gy is administered in more than half of cases (1, 9, 10) and the prescription dose has not been standardized. We perform radiotherapy for esophageal cancer at Tokushima University Hospital ; conventionally, two main protocols of 60 Gy/30 fractions/6 weeks and 50.4 Gy/28 fractions/5.6 weeks have been used. Here, we investigate the results of definitive radiotherapy for esophageal cancer at Tokushima University Hospital and clarify the prognostic factors including prescription dose.

Received for publication June 4, 2018 ; accepted September 26, 2018.

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PATIENTS AND METHODS

Patients

The present study was approved by the ethics committee of Tokushima University Hospital (Approval No. 3061).

Seventy-six patients received radical radiotherapy for esophageal cancer between May 2004 and March 2012 at Tokushima University Hospital. Six patients were excluded because there was no follow-up observation. The clinical characteristics of patients are shown in Table 1. The follow-up period was 2-134 months, with a median of 17.2 months. Male : female ratio was 57 : 13 and median age was 69 years (range 44-94). Histologically, 66 cases were squamous cell carcinoma, two cases were adenocarcinoma, and two cases were unknown.

Radiotherapy

All patients underwent three-dimensional conformal radiotherapy. X-rays had been applied using opposing portal, three portal or four portal irradiation for a daily fraction of 1.8-2.0 Gy delivered five times per week for a total dose of 50-64 Gy (median 60 Gy). In this study, a different dose of 50.4 Gy/28 fractions or 60 Gy/30 fractions was mainly delivered to a patient at random. When opposing portal irradiation was used, the irradiation field was changed to avoid the spinal cord after about 40 Gy. Clinical target volume basically encompassed primary lesion and lymph nodes metastasis with adequate margin and prophylactic regional lymph node area.

Table 1. Characteristics of patients

Age	
Median (range)	69 (44-94)
Sex	
Male	57
Female	13
PS (ECOG)	
0	27
1	36
2	7
Location	
Cervical	7
Thoracic	56
Abdominal	3
Cervical - Thoracic	4
Pathological type	
Squamous cell carcinoma	66
Adenocarcinoma	2
Unknown	2
T (UICC 8th)	
1	16
2	8
3	14
4a	5
4b	27
N (UICC 8th)	
0	24
1	20
2	21
3	5
Stage (UICC 8th)	
Ⅰ	16
Ⅱ	9
Ⅲ	10
Ⅳa	35

ECOG, Eastern Cooperative Oncology Group ; PS, performance status ; UICC, Union for International Cancer Control

Chemotherapy

Concurrent chemotherapy was performed in 62 cases, neoadjuvant chemotherapy in 25 cases, and adjuvant chemotherapy in 39 cases (Table 2). Chemotherapy regimens were DFP (docetaxel, 5-fluorouracil and cisplatin), FP (5-fluorouracil and cisplatin), tegafur/gimeracil/oteracil potassium and nedaplatin plus 5-fluorouracil.

Outcome and toxicity analysis

Overall survival was defined as the period from the date of the first RT fraction to the date of death. Survival was calculated with Kaplan-Meier methods, and the significance of differences was examined with the log-rank test. Cox's proportional hazard model was used for multivariate analysis. Differences were defined as statistically significant at $p < 0.05$. Late radiation morbidity was defined as a complication occurring more than 90 days after completion of RT. Grading of the morbidity was performed according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring schema. We used the Statistical Package for Social Science (SPSS version 25 ; International Business Machines Corporation, Armonk, NY, USA) for all analyses.

Table 2. Setting of chemotherapy

	n (%)
Neoadjuvant chemotherapy	25 (35.7)
Concurrent chemotherapy	62 (88.6)
Adjuvant chemotherapy	39 (55.7)

RESULTS

Figure 1 shows the local control rate for all patients and for each stage. The 5-year local control rate of stage I, II, III, and IVA was 71.4%, 100%, 9.4%, and 38.5%, respectively. Univariate analysis

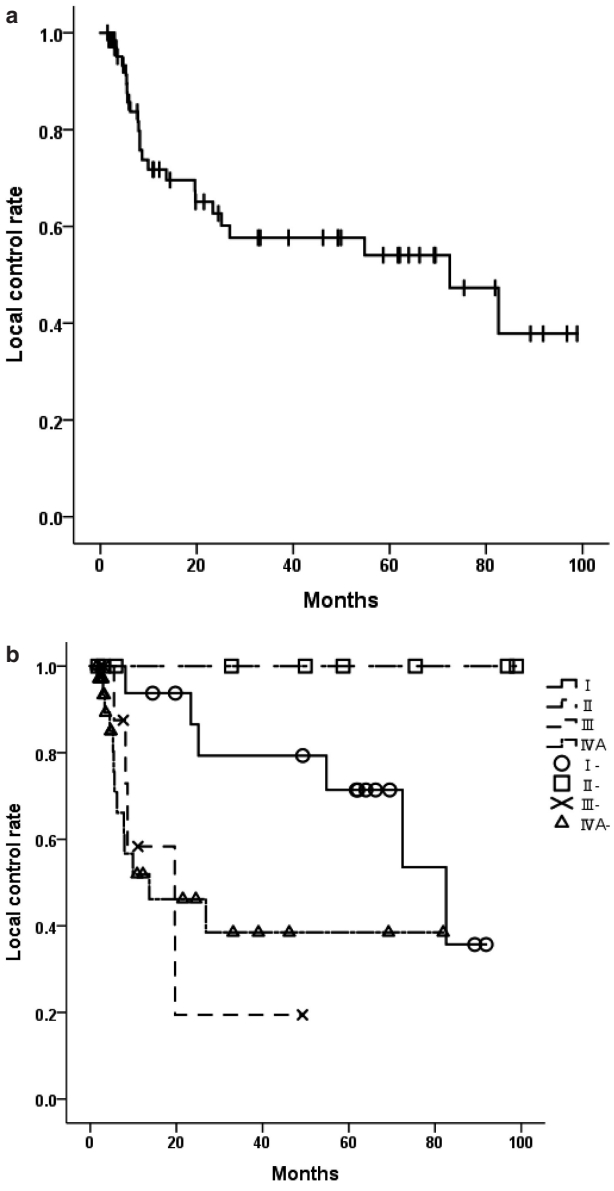

Fig. 1
(a) Local control rate of all patients.
(b) Local control rate according to the stage.

revealed that stage and neoadjuvant chemotherapy were significant prognostic factors of local control (Table 3), although only stage was a significant factor in multivariate analysis (Table 4). Local recurrence occurred in 24 patients and lymph node recurrence within the irradiation field was observed in 8 patients. Lymph node metastasis outside the irradiation field occurred in 12 cases and distant metastasis was present in 20 cases. About half of the cases were judged to be complete response after radiotherapy, and only one salvage surgery was done.

The 5-year overall survival rate for stage I, II, III, and IVA was 81.3%, 71.4%, 0%, and 9.1%, respectively (Figure 2). Univariate analysis of 5-year overall survival revealed that performance status, clinical stage, and neoadjuvant chemotherapy were significant prognostic factors of overall survival (Table 3), and these factors remained significant in multivariate analysis (Table 5). No significant relationship between radiation dose and clinical outcomes was observed.

Table 6 shows clinical characteristics each of Stage Ⅰ／Ⅱ and

Table 3. Univariate analysis of 5-year local control rate and overall survival rate

Factor	n	5-year LC rate (%)	*p*-value	5-year OS rate (%)	*p*-value
Age					
< 69	34	67.0	0.224	38.3	0.582
≧69	36	40.0		31.8	
Sex					
Male	57	51.8	0.657	36.1	0.872
Female	13	60.6		30.8	
PS					
0-1	63	54.0	0.819	37.5	0.040
2-3	7	60.0		14.3	
Stage					
Ⅰ/Ⅱ	25	79.3	<0.001	78.3	<0.001
Ⅲ/Ⅳ	45	34.5		8.6	
Location					
Cervical	11	66.7	0.648	25.0	0.518
Thoracic-Abdominal	59	52.3		36.3	
neoadjuvant chemotherapy					
yes	25	27.3	0.01	12.5	<0.001
no	45	65.9		48.8	
concurrent chemotherapy					
yes	62	56.0	0.899	32.3	0.238
no	8	44.4		57.1	
adjuvant chemotherapy					
yes	39	54.8	0.589	26.9	0.301
no	31	53.3		44.1	
Dose					
< 60 Gy	29	51.8	0.497	41.0	0.109
≧60 Gy	41	55.4		30.9	
Treatment period					
< 44 days	16	58.6	0.830	46.7	0.216
≧44 days	54	52.1		31.5	

LC, Local control ; OS, Overall survival
p-value was calculated using log-rank test.

Table 4. Multivariate analysis of 5-year local control rate

Factor	n	*p*-value	Hazard Ratio	95%CI
Stage				
Ⅰ/Ⅱ	25	0.003	1.00	
Ⅲ/Ⅳ	45		4.95	1.71-14.33
Neoadjuvant chemotherapy				
yes	25	0.079	1.00	
no	45		0.47	0.20-1.09

p-value was calculated using cox's proportional hazard model.

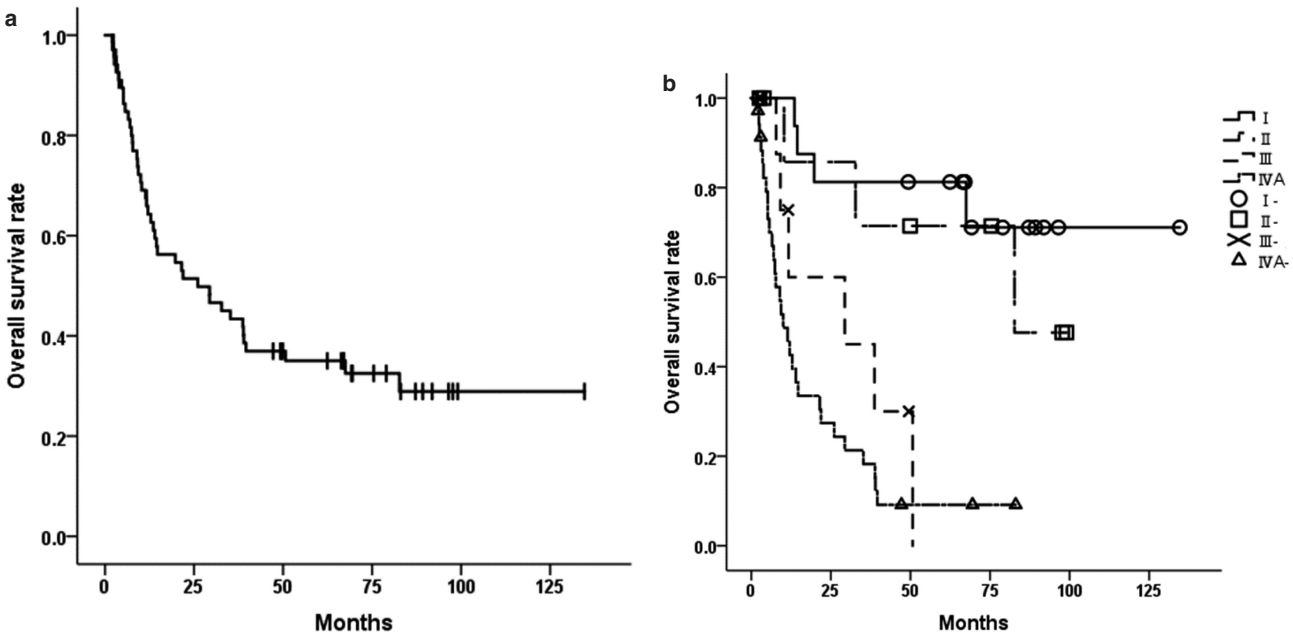

Fig. 2
(a) Overall survival rate of all patients.
(b) Overall survival rate according to the stage.

Table 5. Multivariate analysis of 5-year overall survival rate

Factor	n	*p*-value	Hazard Ratio	95%CI
PS				
0-1	63	0.008	1.00	
2-3	7		3.44	1.38-8.55
Stage				
Ⅰ/Ⅱ	25	<0.001	1.00	
Ⅲ/Ⅳ	45		6.44	2.71-15.33
Neoadjuvant chemotherapy				
yes	25	0.002	1.00	
no	45		0.36	0.19-0.69

p-value was calculated using cox's proportional hazard model.

Stage Ⅲ／Ⅳ. There were more patients undergoing neoadjuvant chemotherapy in Stage Ⅲ／Ⅳ, although no significant difference was observed in other factors. Univariate analysis of 5-year overall survival revealed that performance status and neoadjuvant chemotherapy were significant prognostic factors in Stage Ⅲ／Ⅳ, and neoadjuvant chemotherapy was a significant prognostic factor in Stage Ⅰ／Ⅱ (Table 7). In multivariate analysis, performance status and neoadjuvant chemotherapy were significant prognostic factors in Stage Ⅲ／Ⅳ (Table 8).

Late radiation morbidity of Grade 5 occurred in four cases ; three patients died of radiation-induced lung injury and the other patient died of hematemesis due to esophageal perforation. Fibrocystic change of the lungs that showed a past history of interstitial pneumonia was observed on computed tomography before radiotherapy in three patients who developed Grade 5 radiation-induced lung injury.

DISCUSSION

The treatment results of RT for patients with esophageal cancer at Tokushima University Hospital were similar to those of previous reports (1, 11). The outcome of patients with advanced esophageal cancer is still not satisfactory and reports indicate that there has been no significant improvement in treatment outcomes of esophageal cancer since the 2000s (9, 7) . In the present study, a history of neoadjuvant chemotherapy was related to poor prognosis regardless of Stage. Possible reasons for this association include cases in which surgery could not be performed because the tumor did not shrink and crossover resistance of chemotherapy and radiotherapy. The long-term results of NRG (National Surgical Adjuvant Breast and Bowel Project, Radiation Therapy Oncology Group, Gynecologic Oncology Group) Oncology Radiation Therapy Oncology Group 0246 demonstrate promising efficacy of a selective surgical resection strategy in patients with esophageal cancer after definitive concurrent chemoradiotherapy (12). In addition, a report on preoperative chemoradiotherapy for resectable esophageal cancer showed that chemoradiotherapy plus surgery significantly reduced 3-year mortality, but postoperative mortality was signifi-

Table 6. Characteristics of Stage Ⅰ / Ⅱ and Stage Ⅲ / Ⅳ

Factor	Sum (n)	Stage Ⅰ / Ⅱ (n)	Stage Ⅲ / Ⅳ (n)	*p*-value
Age				
< 69	34	23	11	0.624
≧69	36	22	14	
Sex				
Male	57	20	37	1.000
Female	13	5	8	
PS				
0-1	63	23	40	1.000
2-3	7	2	5	
Location				
Cervical	11	2	9	0.306
Thoracic-Abdominal	59	23	36	
neoadjuvant chemotherapy				
yes	25	4	21	0.018
no	45	21	24	
concurrent chemotherapy				
yes	62	20	42	0.124
no	8	5	3	
adjuvant chemotherapy				
yes	39	10	29	0.078
no	31	15	16	
Dose				
< 60 Gy	29	11	18	0.803
≧60 Gy	41	14	27	
Treatment period				
< 44 days	16	8	8	0.236
≧44 days	54	17	37	

p-value was calculated using Fisher's exact test.

cantly increased by neoadjuvant chemoradiotherapy (13, 14). However, these studies contain many cases of adenocarcinoma, and it is unclear whether similar results will be obtained in Japan where squamous cell carcinoma is dominant. A three-arm phase III trial comparing cisplatin plus 5-FU (CF) versus docetaxel, cisplatin plus 5-FU versus RT plus CF as preoperative therapy for locally advanced esophageal cancer (JCOG1109) (15) is being conducted in Japan and the results are expected to lead to the development of new treatment strategies for esophageal cancer.

In the present study, a different dose of 50.4 Gy/28 fractions or 60 Gy/30 fractions was delivered to a patient at random, and no significant relationship between radiation dose and clinical outcomes was observed. Further research is necessary to determine the optimal dose of radiotherapy for esophageal cancer in Japan.

It has been previously reported that the occurrence of radiation-induced lung injury is associated with radiation dose and volume of lungs ; in particular, low-dose factors such as V20 Gy (volume percentage of the lungs that 20 Gy or greater are irradiated) and V10 Gy are regarded as important (16-18). Guidelines of JASTRO in Japan recommend that V20 Gy of the lungs should be 30-35% or less ; however, the V20 Gy of the lungs of three patients who developed Grade 5 radiation-induced lung injury in the present study was 23.4%, 18.3% and 17.3%, respectively. Except for these three patients, interstitial pneumonia was not observed in the pretreatment computed tomography. Thus, in patients with a past history of interstitial pneumonia, even if the dose to the lungs is low there is a possibility of causing severe radiation-induced lung injury and strict attention should be paid to the indication of RT.

There are several limitations in the present study. It was a retrospective study in a single institute and the number of cases was small. There was no strict decision regarding radiation field, and various regimens were used for chemotherapy.

In conclusion, the results of definitive radiotherapy for esophageal cancer in stage I/II at Tokushima University Hospital were similar to those of previous reports. However, treatment results of the patients in stage III/IV were not satisfactory, and those who could not undergo surgery after neoadjuvant chemotherapy had the worst prognosis. The results of large-scale randomized trials in Japan are expected to drive the development of new treatment strategies to improve the prognosis of locally advanced esophageal cancer.

CONFLICT OF INTEREST

All authors have no financial relationships to disclose for this study.

REFERENCES

1. Tachimori Y, Ozawa S, Numasaki H, Ishihara R, Matsubara H, Muro K, Oyama T, Toh Y, Udagawa H, Uno T, Registration Committee for Esophageal Cancer of the Japan Esophageal S : Comprehensive Registry of Esophageal Cancer in Japan, 2010. Esophagus 14 : 189-214, 2017
2. Nomura M, Kato K, Ando N, Ohtsu A, Muro K, Igaki H, Abe T, Takeuchi H, Daiko H, Gotoh M, Kataoka K,

Table 7. Univariate analysis of 5-year overall survival rate by Stage

Factor	Stage Ⅰ/Ⅱ (%)	*p*-value	Stage Ⅲ/Ⅳ (%)	*p*-value
Age				
< 69	88.9	0.101	15.1	0.800
≧69	71.4		0.0	
Sex				
Male	83.3	0.112	6.5	0.381
Female	60.0		12.5	
PS				
0-1	81.0	0.278	9.8	0.039
2-3	50.0		0.0	
Location				
Cervical	100.0	0.616	14.3	0.819
Thoracic-Abdominal	77.3		6.3	
neoadjuvant chemotherapy				
yes	50.0	0.039	5.0	0.026
no	84.2		13.9	
concurrent chemotherapy				
yes	77.8	0.667	9.0	0.319
no	80.0		0.0	
adjuvant chemotherapy				
yes	87.5	0.687	7.9	0.662
no	73.3		10.9	
Dose				
< 60 Gy	100.0	0.136	0.0	0.111
≧60 Gy	64.3		12.1	
Treatment period				
< 44 days	58.7	0.344	12.5	0.680
≧44 days	75.0		8.7	

p-value was calculated using log-rank test.

Table 8. Multivariate analysis of 5-year overall survival rate of Stage Ⅲ/Ⅳ

Factor	n	*p*-value	Hazard Ratio	95%CI
PS				
0-1	63	0.014	1.00	
2-3	7		3.57	1.30-9.80
Neoadjuvant chemotherapy				
yes	25	0.012	1.00	
no	45		0.41	0.20-0.82

p-value was calculated using cox's proportional hazard model.

Wakabayashi M, Kitagawa Y : Comparison between neoadjuvant chemotherapy followed by surgery and definitive chemoradiotherapy for overall survival in patients with clinical Stage II/III esophageal squamous cell carcinoma (JCOG1406-A). Jpn J Clin Oncol 47 : 480-486, 2017

3. Kato K, Muro K, Minashi K, Ohtsu A, Ishikura S, Boku N, Takiuchi H, Komatsu Y, Miyata Y, Fukuda H, Gastrointestinal Oncology Study Group of the Japan Clinical Oncology G : Phase II study of chemoradiotherapy with 5-fluorouracil and cisplatin for Stage II-III esophageal squamous cell carcinoma : JCOG trial (JCOG 9906). Int J Radiat Oncol Biol Phys 81 : 684-90, 2011
4. Ando N, Kato H, Igaki H, Shinoda M, Ozawa S, Shimizu H, Nakamura T, Yabusaki H, Aoyama N, Kurita A, Ikeda K, Kanda T, Tsujinaka T, Nakamura K, Fukuda H : A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol 19 : 68-74, 2012
5. Ariga H, Nemoto K, Miyazaki S, Yoshioka T, Ogawa Y, Sakayauchi T, Jingu K, Miyata G, Onodera K, Ichikawa H, Kamei T, Kato S, Ishioka C, Satomi S, Yamada S : Prospective comparison of surgery alone and chemoradiotherapy with selective surgery in resectable squamous cell carcinoma of the esophagus. Int J Radiat Oncol Biol Phys 75 : 348-56, 2009
6. Wong SK, Chiu PW, Leung SF, Cheung KY, Chan AC, Au-Yeung AC, Griffith JF, Chung SS, Ng EK : Concurrent chemoradiotherapy or endoscopic stenting for advanced squamous cell carcinoma of esophagus : a case-control study.

Ann Surg Oncol 15 : 576-82, 2008
7. Jingu K, Umezawa R, Matsushita H, Sugawara T, Kubozono M, Yamamoto T, Ishikawa Y, Kozumi M, Takahashi N, Katagiri Y, Kadoya N, Takeda K : Chemoradiotherapy for T4 and/or M1 lymph node esophageal cancer : experience since 2000 at a high-volume center in Japan. Int J Clin Oncol 21 : 276-282, 2016
8. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, Okawara G, Rosenthal SA, Kelsen DP : INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer : high-dose versus standard-dose radiation therapy. J Clin Oncol 20 : 1167-74, 2002
9. Nishimura Y, Jingu K, Itasaka S, Negoro Y, Murakami Y, Karasawa K, Kawaguchi G, Isohashi F, Kobayashi M, Itoh Y, Ariga T : Clinical outcomes of radiotherapy for esophageal cancer between 2004 and 2008 : the second survey of the Japanese Radiation Oncology Study Group (JROSG). Int J Clin Oncol 21 : 88-94, 2016
10. Nishimura Y, Koike R, Ogawa K, Sasamoto R, Murakami Y, Itoh Y, Negoro Y, Itasaka S, Sakayauchi T, Tamamoto T : Clinical practice and outcome of radiotherapy for esophageal cancer between 1999 and 2003 : the Japanese Radiation Oncology Study Group (JROSG) Survey. Int J Clin Oncol 17 : 48-54, 2012
11. Anbai A, Koga M, Motoyama S, Jin M, Shibata H, Hashimoto M : Outcomes of patients with stage IVA esophageal cancer (Japanese classification) treated with definitive chemoradiotherapy. Jpn J Radiol 31 : 270-6, 2013
12. Swisher SG, Moughan J, Komaki RU, Ajani JA, Wu TT, Hofstetter WL, Konski AA, Willett CG : Final Results of NRG Oncology RTOG 0246 : An Organ-Preserving Selective Resection Strategy in Esophageal Cancer Patients Treated with Definitive Chemoradiation. J Thorac Oncol 12 : 368-374, 2017
13. Fiorica F : Preoperative chemoradiotherapy for oesophageal cancer : a systematic review and meta-analysis. Gut 53 : 925-930, 2004
14. Tepper J, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, Goldberg R, Kiel K, Willett C, Sugarbaker D, Mayer R : Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer : CALGB 9781. J Clin Oncol 26 : 1086-92, 2008
15. Nakamura K, Kato K, Igaki H, Ito Y, Mizusawa J, Ando N, Udagawa H, Tsubosa Y, Daiko H, Hironaka S, Fukuda H, Kitagawa Y, Japan Esophageal Oncology Group/Japan Clinical Oncology G : Three-arm phase III trial comparing cisplatin plus 5-FU (CF) versus docetaxel, cisplatin plus 5-FU (DCF) versus radiotherapy with CF (CF-RT) as preoperative therapy for locally advanced esophageal cancer (JCOG1109, NExT study). Jpn J Clin Oncol 43 : 752-5, 2013
16. Tsujino K, Hirota S, Endo M, Obayashi K, Kotani Y, Satouchi M, Kado T, Takada Y : Predictive value of dose-volume histogram parameters for predicting radiation pneumonitis after concurrent chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys 55 : 110-115, 2003
17. Kumar G, Rawat S, Puri A, Sharma MK, Chadha P, Babu AG, Yadav G : Analysis of dose-volume parameters predicting radiation pneumonitis in patients with esophageal cancer treated with 3D-conformal radiation therapy or IMRT. Jpn J Radiol 30 : 18-24, 2012
18. Nomura M, Kodaira T, Furutani K, Tachibana H, Tomita N, Goto Y : Predictive factors for radiation pneumonitis in oesophageal cancer patients treated with chemoradiotherapy without prophylactic nodal irradiation. Br J Radiol 85 : 813-8, 2012