Patterns of relapse after definitive chemoradiotherapy in stage II/III (non-T4) esophageal squamous cell carcinoma

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Running head: Relapse after chemoradiotherapy for esophageal squamous cell carcinoma

Key words: Esophageal squamous cell carcinoma; chemoradiation; Recurrence; Salvage treatment.

Abstract

Purpose: The purpose of this study was to investigate the utility of surveillance after definitive chemoradiotherapy (dCRT) in patients with squamous cell carcinoma.

Methods: Patients who underwent dCRT for stage II/III (excluding T4) esophageal squamous cell carcinoma were analyzed. First failures following complete response were classified into luminal relapse (LR), regional relapse (RR), distant metastasis (DM), new cancer diagnosed by esophagogastroduodenoscopy (NC-E), and new cancer other than NC-E (NC-O). We focused on LR, RR and NC-E, and analyzed their frequency, timings and survival outcomes after local treatments.

Results: Among 302 patients treated with dCRT, 204 achieved complete response. Numbers of patients who recurred with LR, RR, DM, NC-E and NC-O were 28 (14% of 204), 13 (6%), 39 (19%), 34 (17%) and 16 (8%). Ninety-three percent of LRs were diagnosed within 3 years after dCRT, and all RRs were within 2 years. Annual odds of NC-E did not decrease over time. Twenty-three patients with LR, 6 with RR and 32 with NC-E underwent local treatment, and their median overall survivals were 49.2, 19.5 and 108.9 months.

Conclusion: Surveillance with esophagogastroduodenoscopy may be important in the first 3 years after dCRT to detect LR and to detect NC-E beyond 3 years.

Introduction

New cases of esophageal cancer are estimated to be 455,800, and 400,200 patients died from esophageal cancer worldwide in 2012[1]. The incidence of esophageal cancer is high in Eastern Asia and Eastern and Southern Africa[1, 2], with squamous cell carcinoma being the most common histological type in these geographical areas. For locally advanced esophageal squamous cell carcinoma, standard treatment is surgery with preoperative chemotherapy or chemoradiotherapy [3-6]. Definitive chemoradiotherapy (dCRT) has also been developed as a treatment option, especially for patients who are not fit for surgery or who have been denied surgery [7-11]. Because recent studies focusing on adenocarcinoma-dominant population revealed that local-regional relapse occurs more frequently after dCRT[12] than after surgery with preoperative chemoradiotherapy[13], surveillance for local-regional relapse after dCRT is recognized to be important[14].

Similarly, for patients with esophageal squamous cell carcinoma, surveillance after dCRT is recommended as well[14, 15]. However, clinical utility of surveillance has not been studied thoroughly for these patients. In addition to relapse, patients with esophageal squamous cell carcinoma are at high risk of developing other cancers (i.e., head and neck cancer, new esophageal cancer, gastric cancer and others) [16], and esophagogastroduodenoscopy occasionally finds a new cancer (NC-E, new cancer diagnosed by esophagogastroduodenoscopy). To assess the outcomes of surveillance, therefore, it seems useful to find the incidence of relapse and NC-E using the

database at the National Cancer Center Hospital (Tokyo, Japan) including a large number of patients who were treated with dCRT and followed in a standardized way.

Although surgery is considered as a standard treatment[14, 17, 18] for local-regional relapse after dCRT, patients do not always undergo surgery due to various reasons (i.e., patient's condition and choice, and other reasons) but sometimes receive other local therapies, such as endoscopic treatment[19] and chemoradiotherapy. However, outcomes of each salvage treatment for esophageal squamous cell carcinoma have not been well documented. Assessment of treatment outcomes for local-regional relapse and NC-E are also important in terms of surveillance and salvage strategy after dCRT.

To investigate the clinical utility of surveillance after achieving complete response by dCRT in patients with squamous cell carcinoma, we assessed frequencies of local-regional relapse and NC-E after clinical complete response, sensitivities of surveillance modalities, and the outcomes of salvage treatments.

Materials and Methods

Patients' selection

We retrospectively surveyed patients who were diagnosed to have stage II/III (excluding T4) (American Joint Commission on Cancer/International Union against Cancer [AJCC/UICC] 6th edition) esophageal squamous cell carcinoma between 2000 and 2011, and received dCRT at the National Cancer Center

Hospital (Tokyo, Japan). We excluded patients who had double cancer other than esophageal squamous cell carcinoma before dCRT and/or received chemoradiotherapy as a salvage treatment for recurrent disease after surgery. Then, we identified patients who achieved complete response after dCRT as main participants of this study.

Definitive chemoradiotherapy

dCRT consisted of radiotherapy and concurrent chemotherapy. Most of the patients received radiotherapy with a total dose of 60 Gy in 30 fractions over 6 weeks, in which radiotherapy (40 Gy) for elective mediastinal and perigastric lymph nodes were routinely performed. Radiotherapy for cervical lymph nodes was performed for an upper thoracic primary tumor and that for celiac lymph nodes was performed for a lower thoracic primary tumor. Three-dimensional computed tomography (CT) or radiographic simulation contoured 2-dimensional anterior–posterior opposed fields and a bilateral oblique boost field. Some patients received 50.4-Gy radiotherapy in 28 fractions. Physicians preferred 50.4-Gy radiotherapy for patients who were fit for salvage surgery. Three-dimensional treatment planning was required for the 50.4-Gy radiotherapy. A 3- or 4-field technique was recommended for middle or lower thoracic esophagus tumors. With 60-Gy radiotherapy, the most frequently used chemotherapy was 5-FU (700 mg/m^2/day on days 1–4) and cisplatin (70 mg/m^2 on day 1) in monthly cycles. A small number of patients received monthly cycles of 5-FU (800 mg/m^2/day on days 1–5) plus nedaplatin (90 mg/m^2 on day 1) or regimen of docetaxel alone (10

mg/m^2 on days 1, 8, 15, 22, 29 and 36). Patients who underwent 50.4-Gy radiotherapy, received monthly cycles of 5-FU (1000 mg/m^2/day on days 1-4) and cisplatin (75 mg/m^2 on day 1), and a few patients received monthly cycles of S-1 (60-80 mg/m^2 /day on days 1-14) plus cisplatin (75 mg/m^2 on day 1).

Surveillance after dCRT and salvage strategy

After dCRT, patients underwent esophagogastroduodenoscopy and contrast enhanced CT to assess response to dCRT. Clinical response to dCRT was evaluated by CT and esophagogastroduodenoscopy with biopsy, and complete response was defined as the disappearance of all lesions as well as secondary changes associated with the tumors according to the Japanese classification of esophageal cancer, 10th edition[20]. After patients achieved complete response with dCRT, CT and esophagogastroduodenoscopy were generally repeated every 3–6 months for at least 5 years after dCRT, until relapse or death. Among patients achieving complete response, we classified the patterns of first failure as follows: 1) distant metastasis (DM), metastasis to other organs or distant lymph node metastasis according to the 6th edition of AJCC/UICC staging systems; 2) regional relapse (RR), regional lymph node relapse without DM; 3) luminal relapse (LR), intraluminal relapse at the primary site without DM or RR; 4) new cancer (NC), newly found cancer by esophagogastroduodenoscopy (NC-E) (e.g., hypopharynx cancer, metachronous esophageal cancer at a different site from the primary lesion and so on), and new cancer other than NC-E (NC-

O). We assessed sensitivity of each diagnostic modality for the diagnosis of LR, RR and NC-E.

The most appropriate therapies such as surgery, endoscopic therapy, chemoradiation, for local-regional relapses and NC-Es were determined after a discussion at the multidisciplinary team meeting, and all treatments were performed after obtaining informed consent from the patients. To evaluate the outcomes of salvage therapy for LR, RR and NC-E, recurrent diseases were restaged according to the AJCC/UICC staging system (6^{th} ed.) using all available information including radiological imaging, esophagogastroduodenoscopy and pathological findings obtained by endoscopic therapy or salvage surgery.

Statistical analysis

Time to detection of LR, RR and NC-E was calculated from completion of the initial dCRT. Annual odds of occurrence of LR, RR or NC-E were calculated based on the number of patients who were alive without relapse or NC at the beginning of each year. Sensitivity for the diagnosis of LR, RR and NC-E by each modality was calculated as the percentage of patients who had positive findings out of all patients who were diagnosed to have LR, RR or NC-E. For patients who received local therapy for LR, RR or NC-E, overall survival was counted from the date of diagnosis of LR, RR or NC-E to the date of death, or censored at the final date when survival was confirmed. The Kaplan–Meier method was applied to estimate the probability of survival. Overall survival for patients with relapse or

new cancer by local-treatment types were also calculated. The IBM SPSS statistics 23.0 (IBM, Chicago, IL, USA) was used for statistical analyses. This study was approved by the institutional review board.

Results

Patients' characteristics and treatment

We identified a total of 302 patients who had stage II/III esophageal squamous cell carcinoma without double cancer at the time of diagnosis and completed dCRT between 2000 and 2011. Of these 302 patients, 204 (68 %) achieved clinical complete response. Table 1 shows the characteristics of the 204 patients before the initial dCRT. Patients were primarily males with esophageal squamous cell carcinoma in the middle thoracic esophagus.

Timing of local-regional relapses and NCE after complete response

The details of the clinical course from the initial therapy are shown in Figure 1. The median follow-up time calculated in the survivors was 75.7 months (interquartile range, 53.1–104.7). LR, RR, DM, NC-E and NC-O as the first failure were found in 28 (14%), 13 (6%), 39 (19%), 34 (17%) and 16 (8%) patients, respectively. NCs-E included 16 new esophageal cancers, 9 gastric cancers, 7 hypopharynx cancers, 1 oropharynx cancer and 1 esophagogastric junction cancer. NCs-O were 6 colon cancers, 4 lung cancers, 1 diffuse large B-

cell lymphoma, 1 secondary myelodysplastic syndrome, 1 breast cancer, 1 prostate cancer, 1 cervix uteri cancer and 1 tongue cancer. Time to diagnosis of LR, RR and NC-E after completion of dCRT are shown in Table 2. Most (93%) of LRs were diagnosed within 3 years after dCRT and all RRs were found within 2 years. Table 2 also shows annual odds of LR, RR and NC-E. Annual odds of LR and RR beyond 3 years after dCRT were 1.1% or less. Annual odds of NC-E ranged from 3.3 to 9.1% in the first 5 years.

Sensitivities of surveillance modalities

Sensitivity of esophagogastroduodenoscopy for the diagnosis of LR and NC-E was 100% (28/28 for LR and 34/34 for NC-E), whereas sensitivity of CT was 11% (3/27) for the diagnosis of LR and 0% (0/33) for the diagnosis of NC-E. For RR, sensitivity of CT was 69% (9/13). Of 4 RRs, which were not detected by CT, 2 were diagnosed by positron emission tomography and CT, and 2 were diagnosed by pathology of surgical specimens.

Salvage strategies for local-regional relapses and NC-E and their survival outcomes

Sixty-one (81%) of 75 patients with LR (n = 28), RR (n = 13) and NC-E (n = 34) underwent local treatment such as surgery, endoscopic treatment, chemoradiotherapy (Figure 1). Median survival time from the diagnosis of LR, RR and NC-E were 49.2 months (95% confidence interval [CI]: 11.8–86.5), 19.5

months (95% CI: 8.0–31.1) and 108.9 months (95% CI: 68.9–148.8), respectively, for patients with local treatment (Figure 2). Details on survival outcomes according to the treatment type are shown in Table 3.

Discussion

To the best of our knowledge, our study is the first focusing on surveillance strategy in esophageal squamous cell carcinoma patients after dCRT. A recent study, including 78% of patients with adenocarcinoma, showed that 23% of the patients had local-regional relapse after dCRT, and that median survival time of those treated with salvage surgery was 58.6 months[12]. The National Comprehensive Cancer Network (NCCN) guidelines recommend esophagogastroduodenoscopy surveillance for at least 24 months after dCRT for esophageal and esophagogastric junction cancers[14]. In our study focusing on esophageal squamous cell carcinoma, esophagogastroduodenoscopy detected not only LR but also NC-E even after 24 months, whereas most (93%) of LRs were diagnosed within 3 years of dCRT. Moreover, annual odds of NC-E did not decrease over time. NC-E included not only new esophageal cancer but also other cancers detected with esophagogastroduodenoscopy. New esophageal cancers were moderately frequent (16 out of 204 patients; 8%). On the other hand, the number of hypopharynx (7 out of 204; 3%), oropharynx (1 out of 204; 0.5%), gastric (9 out of 204; 4%) and esophagogastric junction cancers (1 out of 204; 0.5%) was low, and some may say that the low incidence of these cancers cannot justify the use of an invasive procedure. However,

incidence of each cancer included in the NC-E category was clearly higher than in the general population, and we think that esophagogastroduodenoscopy benefit patients diagnosed as NC-E and who had local treatment. A previous study on esophageal adenocarcinoma did not showed the incidence of second malignancy after dCRT; therefore, the importance of surveillance for NC-E in patients with esophageal adenocarcinoma is unknown[12]. Since the sensitivity of CT for the diagnosis of LR and NC-E is low, esophagogastroduodenoscopy should be routinely performed to detect LR and NC-E after dCRT. According to a questionnaire survey conducted in 117 Japanese hospitals, esophagogastroduodenoscopy is performed 4 times or more per year in the 1st year after dCRT in approximately half of the hospitals, and it is repeated for 5 years in most hospitals[21]. Moreover, 63% and 39% of the hospitals continued to perform esophagogastroduodenoscopy for 7 and 10 year, respectively.

Because all RRs were diagnosed within 2 years, we recommend intensive surveillance with CT for at least 2 years after dCRT to detect RR. Some of the RR can be cured by salvage surgery.

Interestingly, not only salvage surgery but also endoscopic therapy saved patients with LR after dCRT, although the majority of the patients had a T3 disease before dCRT. It was anticipated that the recurrent disease might be present in the deep layer of the esophagus where the primary T3 tumor invaded. However, the recurrent luminal lesions were diagnosed as stage 0/I and could be removed by endoscopic treatment in 11 patients, resulting in their median overall survival time from diagnosis of relapse being 49 months. Surgery is usually

considered as the standard treatment for relapse after dCRT[14, 17, 18]. However, considering that postoperative mortality and morbidity increase after dCRT[18], endoscopic treatment can be a good alternative for patients with LR designated as stage 0/I. In the previous study on an esophageal adenocarcinoma dominant cohort, 23 of 64 patients with LR or RR had salvage surgery with a very good prognosis (median overall survival: 58.6 months). However, 41 of 64 patients did not receive salvage surgery. As well as esophageal squamous cell carcinoma, salvage-endoscopic treatment for esophageal adenocarcinoma might be a treatment option for patients with stage 0/I LR but unfit for surgery. However, more data and/or randomized studies are needed to confirm endoscopic treatment as an alternative to salvage surgery.

Our analysis has some limitations. It is a retrospective review and a single-center study. The number of patients with each local therapy was relatively small. We did not review second failures, because patient conditions and available salvage therapy after second failure are different from those after the first failure. For diagnosis of complete response after dCRT, patients received CT and esophagogastroduodenoscopy with biopsy according to the Japanese classification of esophageal cancer, 10th edition, and positron emission tomography–CT was not used as recommended by NCCN guidelines. We did not perform cost analysis because costs of surveillance examination differ in the various regions and may not be generalizable. Finally, our analysis did not have the control group for comparison to prove the importance of surveillance

with esophagogastroduodenoscopy. However, we did not foresee such a study for patients with esophageal squamous cell carcinoma.

In conclusion, more than 90 percent of LRs were diagnosed within 3 years after dCRT, but annual odds of NC-E did not decrease over time. If patients had local treatment for LR or NC-E, their median overall survivals after diagnosis of LRs and NC-E were 49.2 months and 108.9 months. Therefore, intensive surveillance with esophagogastroduodenoscopy may be important in the first 3 years after dCRT to detect LR, and esophagogastroduodenoscopy might be needed to detect NC-E beyond 3 years from dCRT.

Table 1. Characteristics of patients who achieved complete response

	Frequency	
Covariate	Number	%
Age, years		
Median	65	
Range	42–81	
Gender		
Males	170	83
Females	34	17
Tumor Location		
Cervical	18	9
Upper thoracic	35	17
Middle thoracic	99	49
Lower thoracic	50	25
Abdominal esophagus	2	1
Baseline T Stage		
T1	63	31
T2	38	19
T3	103	50
Baseline N Stage		
N0	48	24
N1	156	76
Baseline Stage		
Stage II	134	66
Stage III	70	34
Chemotherapy during radiation treatment		
5-FU and cisplatin	184	90
5-FU and nedaplatin	9	4
S-1 and cisplatin	9	4
Docetaxel	2	1
Total radiation dose		
50.4 Gy	57	28
60.0 Gy	147	72

Baseline staging was based on the AJCC/UICC staging system (6th ed.).

Table 2. Timings of LR, RR and NC-E after definitive chemoradiotherapy

	≤12 months	12 – 24 months	24 – 36 months	36 – 48 months	48 – 60 months	≥60 months	Total
Patients at risk							
Number	204	145	110	91	77	62	-
LR							
Number	20	3	3	1	0	1	28
% of total LR	71.4%	10.7%	10.7%	3.6%	0.0%	3.6%	100.0%
Annual odds	9.8%	2.1%	2.7%	1.1%	0.0%	-	-
RR							
Number	6	7	0	0	0	0	13
% of total RR	46.2%	53.8%	0.0%	0.0%	0.0%	0.0%	100.0%
Annual odds	2.9%	4.8%	0.0%	0.0%	0.0%	-	-
NC-E							
Number	7	6	5	3	7	6	34
% of total NC-E	20.6%	17.6%	14.7%	8.8%	20.6%	17.6%	100.0%
Annual odds	3.4%	4.1%	4.5%	3.3%	9.1%	-	-

Patients at risk: number of patients who are alive without relapse or new cancer at the first date of each period. LR, luminal relapse; RR, regional relapse; NC-E, new cancer found with esophagogastroduodenoscopy.

Table 3. Survival of patients with local therapy according to the treatment type

Failure type Treatment	Stage* (number)	E/N	survival outcomes
LR			
Endoscopic therapy**	0 (7)/I (4)	7/11	MST = 49.2 months
Surgery	I (6)/IIA (6)	8/12	MST = 34.7 months
RR			
Surgery	IIB (2)/III (2)/T0N1 (1)	3/5	MST = 19.5 months
Chemoradiotherapy	T0N1 (1)	1/1	died 68.2 months after RR
NC-E			
Esophageal cancer			
Endoscopic therapy**	0 (7)/I (6)	3/13	MST = not reached
Surgery	I (1)/IIB (1)	0/2	alive 14.7 and 122.1 months after NC-E
Gastric cancer			
Endoscopic therapy**	0 (5)/IA (3)	2/8	MST = 87.2 months after NC-E
Surgery	IIA (1)	1/1	died 43.2 months after NC-E
Hypopharynx cancer			
Endoscopic therapy**	I (4)	1/4	MST = 108.9 months
Surgery	III (1)	1/1	died 5.7 months after NC-E
Radiotherapy alone	II (1)	1/1	died 57.1 months after NC-E
Oropharynx cancer			
Endoscopic therapy**	I (1)	0/1	alive 44.0 months after NC-E
Gastroesophageal junction cancer			

Surgery	I (1)	1/1	died 14.7 months after NC-E

* Relapse and NC-E were restaged according to the AJCC/UICC staging system (6th ed.). ** Types of endoscopic therapy included EMR (9 pts; 6 with Tis and 3 with T1 disease), ESD (1 pts with Tis disease) and PDT (1 pts with Tis disease) for LR; EMR (10 pts; 5 with Tis and 5 with T1 disease), ESD (2 pts with Tis disease) and PDT (1 pts with T1 disease) for new esophageal cancer; EMR (2 pts; 1 with Tis and 1 with T1 disease) and ESD (6 pts; 5 with Tis and 1 with T1 disease) for gastric cancer; EMR (3 pts with T1 disease) and ESD (1 pts with T1 disease) for hypopharynx cancer; and ESD (1 pt with T1 disease) for oropharynx cancer. MST was calculated if 2 or more patients were included and 1 or more patients died in each subgroup. N, number of patients; E, events; LR, luminal relapse; RR, regional relapse; NC-E, new cancer found with esophagogastroduodenoscopy; MST, median survival time; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; PDT, photodynamic therapy; pt, patient.

Figure legends

Figure 1. First failure patterns after clinical complete response. Endoscopic therapy included endoscopic mucosal resection, endoscopic submucosal dissection and photodynamic therapy. Radiotherapy included chemoradiotherapy and radiotherapy alone. dCRT, definitive chemoradiotherapy; NC-E, new cancer found with esophagogastroduodenoscopy; NC-O, new cancer other than NC-E; LR, luminal relapse; RR, regional relapse; DM, distant metastasis.

Figure 2. Kaplan–Meier curves showing overall survival from diagnosis of LR, RR and NC-E for patients with local therapy according to the failure pattern. LR, luminal relapse; RR, regional relapse; NC-E, new cancer found with esophagogastroduodenoscopy; N, number of patients; E, events; MST, median survival time; M, months.

Conflict of interest statement

None declared.

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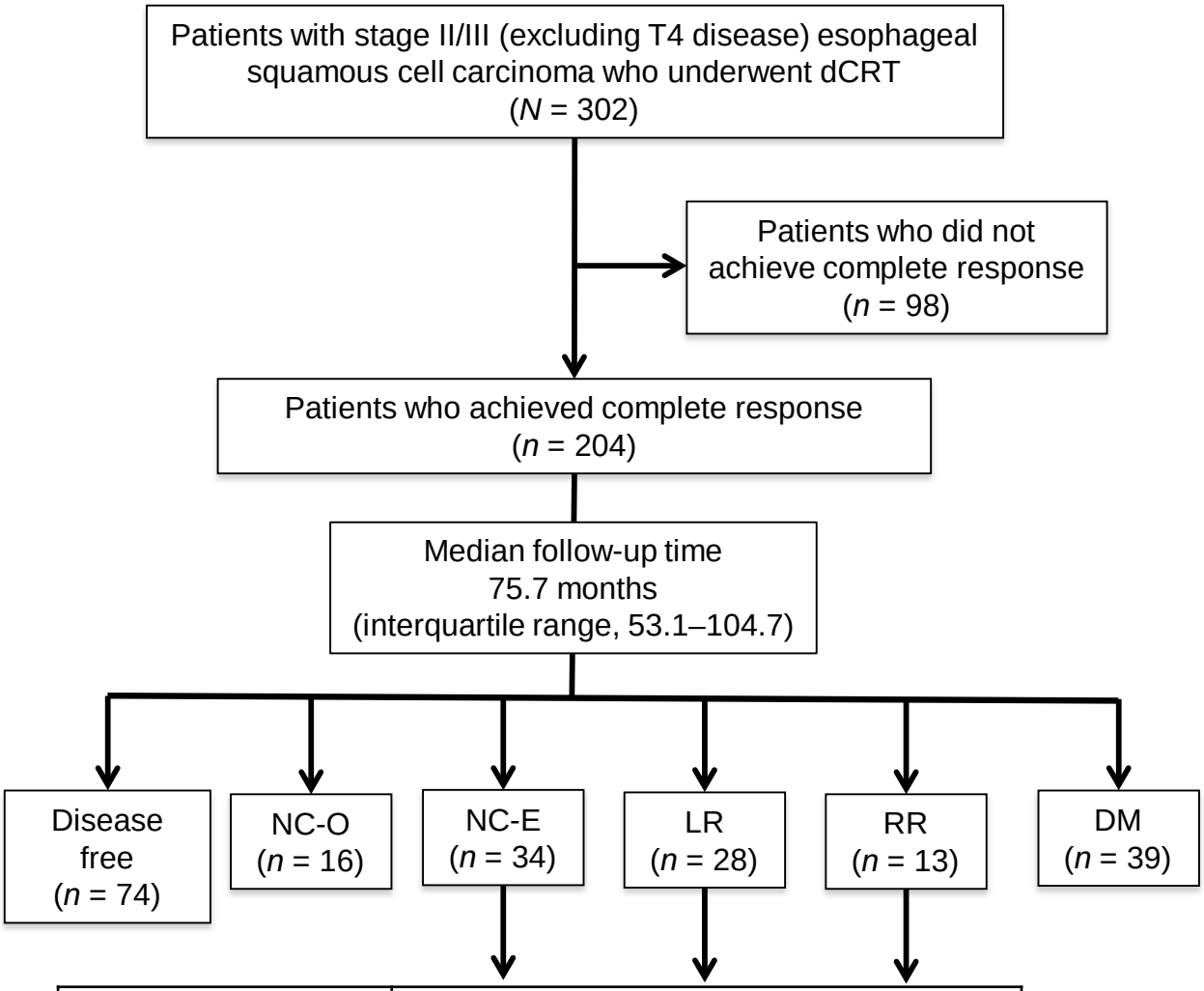
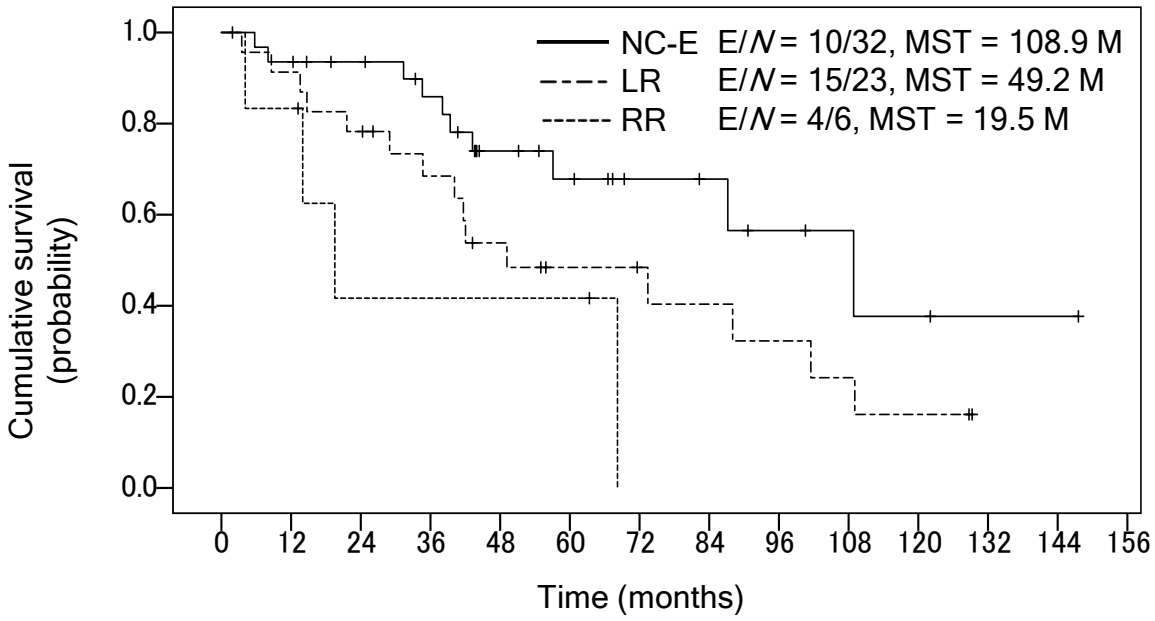


	Local therapy (*n* = 61) (excluding palliative therapy [*n* = 14])		
	NC-E (*n*= 32)	LR (*n* = 23)	RR (*n* = 6)
Endoscopic therapy	26	11	0
Surgery	5	12	5
Radiotherapy	1	0	1

Figure 1.



No. at risk														
	NC-E	32	29	26	22	14	11	7	6	4	3	2	1	1	0
	LR	23	21	18	14	10	7	6	5	4	3	2	0	0	0
	RR	6	5	2	2	2	2	0	0	0	0	0	0	0	0

Figure 2.