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Comparison of definitive chemoradiotherapy and surgery in patients with clinical T1bN0M0 esophageal cancer: A multicenter retrospective study: the Korean Radiation Oncology Group 21-10 trial

cT1bN0M0 식도암 환자의 근치 항암방사선요법과 수술의 비교:
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A multicenter retrospective study:
the Korean Radiation Oncology Group 21-10 trial

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Abstract

Purpose: To compare the treatment outcomes between esophagectomy and definitive chemoradiotherapy (DCRT) in patients with cT1bN0M0 esophageal squamous cell carcinoma (ESCC)

Methods: Medical records of patients with cT1bN0M0 ESCC who were treated at 11 institutions in Korea between January 2010 and April 2020 were retrospectively reviewed. Disease recurrences and overall survival (OS) were compared between patients who had undergone esophagectomy and DCRT.

Results: A total of 333 and 88 patients who had undergone esophagectomy and DCRT, respectively, were included. Patients in the surgery group were significantly younger and had better performance status compared to those in the DCRT group. Clinical complete response (cCR) was achieved in 84 DCRT patients (95.5%) following the treatment. With a median follow-up of 55 months (range, 0.4–134), instances of disease recurrences were observed in 19.2% (64 patients) and 17.0% (15 patients) in the surgery and DCRT groups, respectively. The 5-year locoregional disease-free survival (LRDFS) rate was 86.0% and 75.4% in the surgery and DCRT groups, respectively (p = 0.336). The 5-year distant disease-free survival rate (DDFS) was 84.5% and 92.9% for the surgery and DCRT groups, respectively (p =

0.073). The surgery group displayed a trend toward improved OS (77.8% vs. 65.8%, p = 0.072) on univariate analysis, whereas no significant difference was observed in disease-free survival (DFS) between the two groups (78.5% vs. 74.7%, p = 0.854).

Conclusions: Our study demonstrated that DCRT was equivalent to esophagectomy in terms of LRDFS, DDFS, DFS, and OS rates in patients with cT1bN0M0 ESCC.

Key words: Esophageal cancer, definitive chemoradiotherapy, ER, radical esophagectomy

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Introduction

According to the Global Cancer Observatory, esophageal cancer ranks as the eighth most common cancer and the sixth leading cause of cancer-related death in the world (1). The incidence and mortality rates of esophageal cancer are the highest in Eastern Asia, with over 357,000 cases diagnosed and 319,000 deaths in 2020. According to the National Cancer Registration Statistics in Korea, an overwhelmingly high percentage, 91.4% of esophageal cancer cases were squamous cell carcinoma, which is significantly higher than that reported in Western countries (2). Although studies have reported variable 5-year survival rates in patients with cT1N0M0 tumors, the prognosis of cT1b (submucosal) tumors differs significantly from cT1a (mucosal) tumors due to a significant increase in the lymph node metastasis rate in T1b (3-6). Radical surgery has become the standard of care primarily attributed to the notable risk of lymph node metastasis (20–40%) in cT1b tumors. However, most patients experienced surgical morbidities, such as pulmonary toxicity, anastomotic leakage, or stenosis, as well as various quality-of-life issues following esophagectomy. In patients unwilling or medically unfit to undergo surgery, definitive chemoradiotherapy (DCRT) is another option that can provide satisfactory oncologic outcomes while preserving organ function and quality of life, without the serious surgical complications associated with esophagectomy. However, the equivalence of DCRT results to those of esophagectomy

remains uncertain, because several investigators have reported conflicting results. For instance, Pan *et al*. analyzed 177 cases of T1b esophageal cancer from the Surveillance, Epidemiology, and End Results (SEER) database and concluded that the overall survival (OS) after esophagectomy was superior to that of non-esophagectomy patients (7). However, it is important to note that more than 90% of their patients were of white ethnicity, and approximately 80% had adenocarcinoma, suggesting that their findings could not be extrapolated to Asian patients with squamous cell carcinoma. Esophageal adenocarcinoma and squamous cell carcinoma exhibit differences in response to chemoradiotherapy (CRT), recurrence patterns, and survival rates (8, 9). For example, Ma *et al*. demonstrated in their meta-analysis that the 2- and 5-year OS rates were not significantly different between DCRT and surgery. Furthermore, DCRT appeared to be more effective in patients with esophageal squamous cell carcinoma (ESCC), although surgery showed a tendency toward superiority in cases with stage I or N0 disease (10). In 2021, we conducted a retrospective study to compare survival outcomes between DCRT and esophagectomy in patients with cT1bN0M0 ESCC (11). The study revealed no significance difference between DCRT and surgery in terms of the 5-year survival rate (68.8% vs. 75.8%, $p = 0.135$). However, the relatively small number of patients in the DCRT group limited the reliability of the results. To bolster the statistical power, we subsequently conducted the Korean Radiation Oncology Group (KROG) 21-10 study with a large sample size. This enabled us to conduct a more robust investigation into the equivalence of these two treatment modalities.

Materials and Methods

Study population

We conducted a retrospective review of the medical records of patients with esophageal cancer who were treated at 11 different institutions in South Korea between January 2010 and April 2020. These patients were clinically confirmed to have T1bN0M0 esophageal cancer according to the American Joint Committee on Cancer (AJCC) 8th edition, and met the following criteria: (1) histologically confirmed squamous cell carcinoma by endoscopic biopsy, (2) primary tumor confined to the submucosa without any evidence of invasion into the muscularis propria on endoscopic ultrasound (EUS), (3) no clinical evidence of lymph node or distant organ metastasis, (4) no previous history of chemotherapy and/or radiotherapy within the last 5 years, and (5) age >18 years (12). Patients who were initially staged as cT1aN0M0 and subsequently identified as pT1b after endoscopic resection (ER) were excluded from this study.

Before initiating the treatment, all patients underwent a series of diagnostic procedures, including esophagogastroduodenoscopy (EGD) with biopsy, EUS, chest-abdomen-pelvis computed tomography (CT) scans, and fludeoxyglucose-18 (FDG) positron emission tomography (PET)-CT scans. In addition, endoscopic resections were allowed before DCRT or surgery after the clinical stage was determined as cT1bN0M0. The study protocol was approved by the Institutional Review Boards of all participating institutions and the Korean

Radiation Oncology Group (KROG 21-10).

Treatment modalities

For the surgery group, radical dissection was performed using either the Ivor Lewis, McKeown operation, or transhiatal esophagectomy, with two or three-field lymph node dissection. Patients with tumor stages of T3 or higher, or those with positive lymph nodes following surgical resection, underwent adjuvant treatment in accordance with the guidelines of each respective institution.

Radiotherapy was delivered using either three-dimensional conformal radiation therapy (3D-CRT) or intensity-modulated radiation therapy (IMRT), with a daily fractional dose of 1.8–2.0 Gy. The gross target volume (GTV) was determined using the information from EGD/EUS, chest CT, and PET-CT scans. The clinical target volume (CTV) included the mediastinum and esophagus, with a margin of 3 to 5 cm from the GTV craniocaudally and 0.7 to 1 cm in the radial direction. For tumors located in the cervical/upper thoracic esophagus, or the distal esophagus/gastroesophageal junction (GEJ) area, elective nodal irradiation (ENI) was administered to the supraclavicular or the celiac area, respectively, at the discretion of radiation oncologists at each institution. The planning target volume (PTV) was defined as a further 7 to 10 mm expansion from the CTV.

Concurrent chemotherapy regimens were relatively homogenous and consisted of two main groups: XP (cisplatin 30 mg/m^2 once a week and capecitabine 800 mg/m^2 twice daily

for 5 days per week) or FP (5-fluorouracil 1000 mg/m^2 /day on days 2–5 and cisplatin 60 mg/m^2 on day 1 every 3 weeks). Before concurrent chemoradiotherapy (CCRT), one or two cycles of induction chemotherapy were allowed at the discretion of medical oncologists.

Evaluation of treatment response, treatment toxicity, and follow-up

Initial assessment of treatment response to DCRT was done at a median interval of 30 days after the completion of treatment using EGD with biopsy, chest CT, and PET-CT scans. A clinical complete response (CR) was defined as the complete disappearance of the tumor on endoscopy and biopsy specimens, the absence of new lesions on CT scans, and metabolic CR as evident by PET-CT scans. Metabolic CR was defined as the complete resolution of FDG uptake at the initial tumor site or the presence of diffuse esophagitis within the radiation field, rendering the initial tumor indistinguishable. If these criteria were not met, the response was categorized as non-CR/non-progressive disease (PD) or PD based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and European Organization for Research and Treatment of Cancer PET criteria (13, 14). After the initial assessment, patients underwent regular follow-up examinations, including EGD and CT scans, at intervals of every 3 to 6 months for the first 2 years and then every 6 months for the next 3 years.

In patients who received DCRT, toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (version 5.0). Acute toxicities were monitored up

to 90 days after treatment, whereas late toxicities were defined as those occurring more than 90 days after completion of the treatment. For patients who underwent surgery, postoperative complications were assessed using the Clavien–Dindo classification system, with acute complications occurring within 30 days after the surgery.

Local recurrence was defined differently in the DCRT and surgery groups due to the anatomical changes after esophagectomy. In the DCRT group, local recurrence was defined as histologically confirmed tumor regrowth in the esophagus, whereas it was defined as tumor recurrence at the anastomosis site or the initial tumor bed in the surgery group. Regional recurrence was defined as the presence of failure in the regional lymph nodes in the mediastinum and perigastric areas. Locoregional recurrences included both local and regional recurrences. Celiac nodes were considered regional lymph nodes and supraclavicular nodes were counted as distant metastasis in terms of recurrence patterns. The definitions of disease-free survival (DFS), locoregional disease-free survival (LRDFS), and distant disease-free survival (DDFS) were as the time from the first day of treatment until the first recurrence or patient death of any cause, the time from the first day of treatment until the locoregional recurrence or patient death of any cause, and the time from the first day of treatment until the distant metastasis or patient death of any cause, respectively. And in cases where multiple recurrences were identified simultaneously, each recurrence was counted as an independent event.

Statistical analysis

Patient characteristics between the DCRT and surgery groups were compared using the Student *t*-test, Fisher's exact test, Chi-square test, and Mann-Whitney U test as appropriate. The time from the diagnosis to the start of the treatment was calculated as the interval from the biopsy date to the initial treatment date. Time-to-event end points were estimated using the Kaplan–Meier method, and the log-rank test was used to compare the differences between the curves. All reported *p*-values were two-sided, and the significance level was set at 0.05 for all analyses.

As no more than one prognostic factor with a *p*-value less than 0.1 was identified in the univariable analysis, a multivariable analysis was not conducted. All statistical analyses were performed using the SPSS version 22.0 statistic software package (IBM Corporation, NY, USA).

Results

Patient characteristics

Between January 2010 and April 2020, 421 eligible patients were included in the study: 333 patients in the surgery group and 88 patients in the DCRT group. The baseline characteristics are summarized in Table 1. Patients' ages differed significantly, with a median age of 63 years for the surgery group and 72 years for the DCRT group. The Eastern Cooperative Oncology Group (ECOG) performance status and Charlson Comorbidity Index (CCI) scores varied notably, indicating worse status and higher comorbidities in the DCRT group compared to the surgery. In addition, tumor site distribution demonstrated a significant difference, with the DCRT group having more upper-site tumors in comparison to the surgery group.

The median follow-up duration was 55 months (range, 0.4–137) for the surgery group and 45 months (range, 4–134) for the DCRT group.

Table 1. Patient characteristics.

Characteristics	Surgery (n = 333)	DCRT (n = 88)	*p*-value
Age (years), median (range)	63 (39–79)	72 (44–84)	<0.001
Sex			0.993
Male	314 (94.3%)	83 (94.3%)	
Female	19 (5.7%)	5 (5.7%)	
ECOG			<0.001
0	252 (75.7%)	36 (40.9%)	
1	80 (24.0%)	50 (56.8%)	
2	1 (0.3%)	2 (2.3%)	
CCI			<0.001
0	176 (52.9%)	0 (0%)	
1	95 (28.5%)	0 (0%)	
2	57 (17.1%)	23 (26.1%)	
3	5 (1.5%)	65 (73.9%)	
Tumor site			0.008
Cervical	0 (0%)	2 (2.3%)	
Upper	28 (8.4%)	23 (26.1%)	
Middle	188 (56.5%)	31 (35.2%)	
Lower	117 (35.1%)	32 (36.4%)	
Histologic grade			0.366
G1	26 (7.8%)	10 (11.4%)	
G2	286 (85.9%)	63 (71.5%)	
G3	21 (6.3%)	5 (5.7%)	
GX	0 (0%)	10 (11.4%)	
Follow-up duration (months), median (range)	55 (0.4–137)	45 (4–134)	

Abbreviations: DCRT, definitive chemoradiotherapy, ECOG, Eastern Cooperative Oncology Group; CCI, Charlson Comorbidity Index.

Treatment compliance and complications

Of the 51 patients in the DCRT group who were assessed for receiving DCRT as a treatment option, 18 patients refused surgery, 33 patients were deemed inoperable due to comorbidities. In the DCRT group, the median radiation dose administered was 50.4 Gy (range, 38.0–64.0), and all patients received CCRT according to each institution's protocol. Among these patients, 15 patients (17.0%) underwent ER before DCRT. A total of 87 patients (98.9%) successfully completed the initially planned treatment, whereas one patient did not due to pancytopenia and radiation-induced esophagitis.

The acute and late toxicities of DCRT are detailed in Table 2 Eighteen patients (20.5%) experienced grade 3 or higher acute toxicities related mostly to neutropenia and thrombocytopenia. Among non-hematologic toxicities, radiation-induced esophagitis of grade 3 or higher was observed in four patients (4.5%). Regarding late toxicities, although no patients experienced grade 4 or 5 toxicities, two patients developed grade 3 esophageal stenosis and received balloon dilatation. In addition, two more patients experienced grade 3 cardiac toxicities.

Surgical complications are presented in Table 3. The most common early complications included anastomotic leak and vocal cord palsy resulting from an injury to the recurrent laryngeal nerve. Clavin–Dindo grade 3 or higher complications occurred in 82 patients (24.6%). Surgical mortality was observed in five patients (1.5%); four patients died of shock and one patient died of complicated pneumonia. Pulmonary toxicity and anastomosis

stricture were the most frequently diagnosed complications.

Table 2. Acute and late toxicities of grade 2 or higher in the DCRT group (n = 88).

Toxicities	No. of patients (%)		
	Grade 2	Grade 3	Grade 4
Acute (≤90 days)			
Anorexia	19 (21.6%)	1 (1.1%)	0 (0%)
Nausea	1 (1.1%)	0 (0%)	0 (0%)
Neutropenia	14 (15.9%)	3 (3.4%)	3 (3.4%)
Thrombocytopenia	10 (11.4%)	5 (5.7%)	2 (2.2%)
Dermatitis	0 (0%)	0 (0%)	0 (0%)
Esophagitis	23 (26.1%)	4 (4.5%)	0 (0%)
Late (> 90 days)			
Pneumonia	1 (1.1%)	0 (0%)	0 (0%)
Cardiac toxicity	0 (0%)	2 (2.2%)	0 (0%)
Transesophageal fistula	0 (0%)	0 (0%)	0 (0%)
Esophageal stenosis	2 (2.2%)	2 (2.2%)	0 (0%)

Abbreviations: DCRT, definitive chemoradiotherapy; n, number.

Table 3. Acute and late complications in the surgery group (n = 333).

Toxicities	No. of patients (%)
Acute (≤30 days)	
Grade 0–2	251 (75.4%)
Grade 3	70 (21.0%)
Grade 4	7 (2.1%)
Grade 5	5 (1.5%)
Late (> 30 days)	
Pulmonary toxicity	32 (9.6%)
Cardiac toxicity	1 (0.3%)
Anastomosis site leakage	11 (3.3%)
Anastomosis site stenosis	41 (12.3%)
Fistula	7 (2.1%)

Treatment responses in the DCRT group

All patients in the DCRT group were evaluated for treatment response to DCRT. The median interval between the completion of DCRT and the first response evaluation was 4.3 weeks (range, 2.0–20.9). Eighty-four patients (95.5%) achieved a cCR, and no patients experienced PD following the treatment (Table 4).

Table 4. Tumor response in the DCRT group (n = 88).

Response	No. of patients (%)
CR	84 (95.5%)
Non-CR/non-PD	4 (4.5%)
PD	0 (0%)

Abbreviations: DCRT, definitive chemoradiotherapy; CR, complete response; PD, progressive disease.

Pathologic stages of the surgery group

Among the 333 patients in the surgery group, six patients (1.8%) underwent endoscopic submucosal dissection (ESD) before esophagectomy. The median number of dissected lymph nodes was 36 (range, 4–93). Discrepancies were reported between clinical and pathologic stages (Table 5). Pathologic staging confirmed pT1b in 235 patients (70.6%), with 56.2% (187 out of 333) having a confirmed stage of pT1bN0M0. A pTis–T1aN0M0 stage was observed in 84 patients (25.2%), and the pN1–2 stage was identified in 18.9% of patients. Of the 63 patients with positive lymph nodes, 58 received adjuvant CRT.

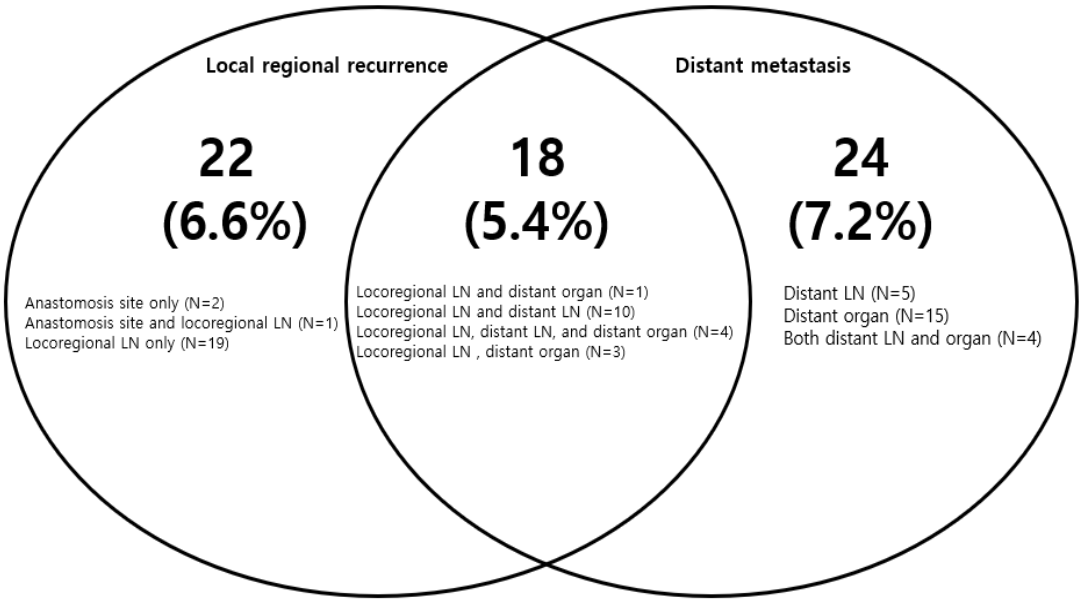
Table 5. Surgical pathologic stages in the surgery group (n = 333).

Pathologic TNM	No. of patients (%)
pTis-T1aN0M0	84 (25.2%)
pT1bN0M0	187 (56.2%)
pT stage	
pTis–T1a	84 (25.2%)
pT1b	235 (70.6%)
pT2	10 (3.0%)
pT3–T4	4 (1.2%)
pN stage	
pN0	270 (81.1%)
pN1	52 (15.6%)
pN2–N3	11 (3.3%)

First failure patterns

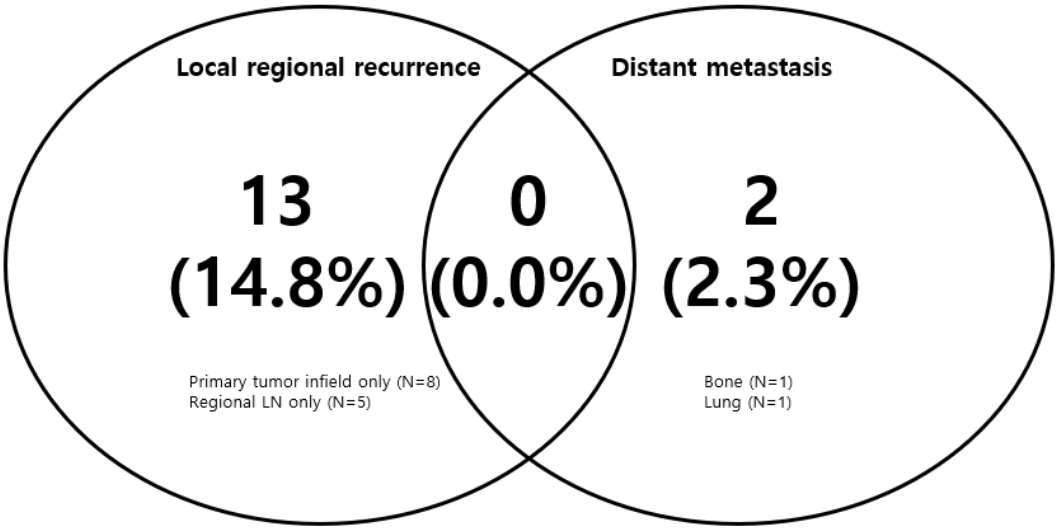
Disease recurrence was observed in 64 patients (19.2%) from the surgery group and 15 patients (17.0%) from the DCRT group (p=0.642) (Figures 1A and 1B). As displayed in Table 6, locoregional recurrence rates as the first event did not significantly differ between the DCRT (14.8%) and surgery groups (12.0%) (p = 0.487). However, distant metastasis as the first event was more common in the surgery group (12.6%) than in the DCRT group (2.3%) (p = 0.005). Sites of distant recurrences in surgery group are displayed in Table 7. In the surgery group, 33 of the 40 patients (82.5%) with locoregional recurrences received salvage treatments, primarily chemotherapy and radiotherapy (42.5%) (Table 8). In the DCRT group, 12 of 13 patients (92.3%) with locoregional recurrences received salvage therapies, predominantly chemotherapy alone (53.8%). Salvage surgery was conducted in four patients (10.0%) in the surgery group and four patients (30.8%) in the DCRT group.

Figure 1A. Patterns of first recurrence in the surgery group.



Abbreviation: LN, lymph node.

Figure 1B. Patterns of first recurrence in the DCRT group.



Abbreviations: DCRT, definitive chemoradiotherapy; LN, lymph node.

Table 6. Locoregional or distant recurrence as the first event.

Pattern of the first recurrence	No. of patients (%)	
	Surgery group (n=333)	DCRT group (n=88)
Locoregional recurrence only	22 (6.6%)	13 (14.8%)
Distant metastasis only	24 (7.2%)	2 (2.3%)
Both locoregional recurrence and distant metastasis	18 (5.4%)	0 (0%)

Abbreviations: DCRT, definitive chemoradiotherapy.

Table 7. Patterns of distant recurrence in the surgery group

Site of distant recurrence	No. of patients (n=42)
Distant lymph node	
Supraclavicular lymph node	11
Abdominal lymph node	3
Supraclavicular lymph node and thoracic lymph node	1
Supraclavicular lymph node and cervical neck node	3
Distant organ	
Liver	3
Lung	7
Bone	2
Pleura	3
Multiple sites	
Supraclavicular lymph node and chest wall	1
Lung and bone	1
Supraclavicular lymph node, lung, liver	1
Supraclavicular lymph node and lung	3
Lung and pleura	1
Pleura and liver	1
Pleura and bone	1

Abbreviations: n, number.

Table 8. Salvage treatments for locoregional recurrence in the surgery and DCRT groups.

Treatment modality	No. of patients (%)	
	Surgery group (n = 40)*	DCRT group (n = 13)
CCRT	17 (42.5%)	1 (7.7%)
Chemotherapy alone	8 (20%)	7 (53.8%)
RT alone	4 (10%)	0 (0%)
Surgery alone	2 (5%)	2 (15.4%)
Surgery followed by RT	0 (0%)	0 (0%)
Surgery followed by CCRT	2 (5%)	0 (0%)
Surgery followed by chemotherapy	0 (0%)	2 (15.4%)
No treatment	7 (17.5%)	1 (7.7%)

Abbreviations: DCRT, definitive chemoradiotherapy; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; n, number.

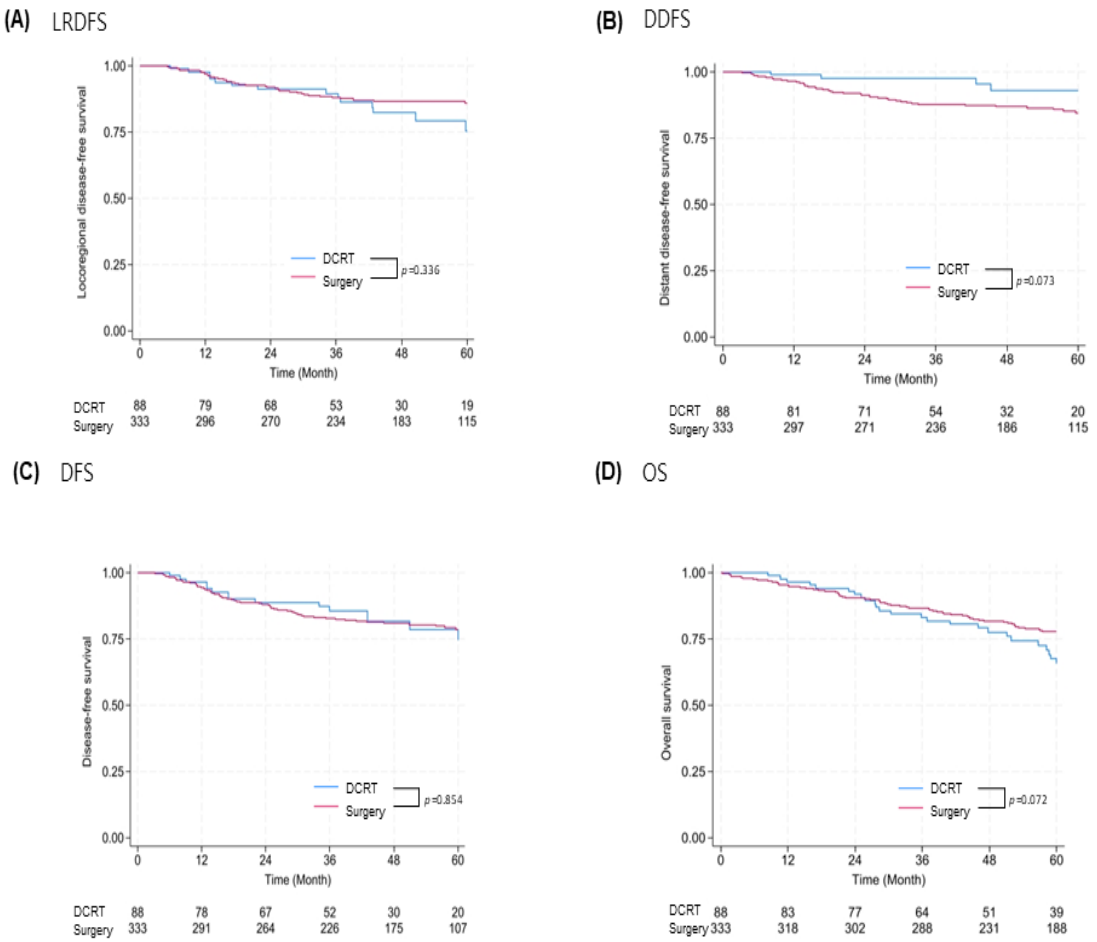
*includes 22 patients who had synchronous distant metastases.

Survival outcomes

No significant difference was observed in LRDFS and DDFS between the DCRT and surgery groups (5-year LRDFS: 75.4% vs. 86.0%, $p = 0.336$; 5-year DDFS: 92.9% vs. 84.5%, $p = 0.073$) (Figure 2A and B). Regarding OS and DFS, no significant differences were observed between the two groups, with a 5-year OS rate of 65.8% for DCRT vs. 77.8% for surgery ($p = 0.072$), and a 5-year DFS rate of 74.7% for DCRT vs. 78.5% for surgery ($p = 0.854$) (Figure 2C and D).

The univariable analysis for LRDFS, DFS, DDFS, and OS are presented in Table 9. Age was the only significant prognostic factor for DFS (hazard ratio [HR], 1.860 for patients >60 years, 95% confidence interval [CI], 1.164–2.970, $p = 0.009$). The treatment modality had no significant impact on LRDFS, DDFS, DFS, and OS.

Figure 2. Kaplan–Meier curves for (A) LRDFS, (B) DDFS, (C) DFS, and (D) OS in the surgery and DCRT groups.



Abbreviations: DCRT, definitive chemoradiotherapy; LRDFS, locoregional disease-free survival; DMFS, distant disease-free survival; DFS, disease-free survival; OS, overall survival.

Table 9. Univariable and multivariable analyses for survival outcomes.

Variables		Locoregional disease-free survival			Disease-free survival			Distant disease-free survival						Overall survival		
		Univariable			Univariable			Univariable			Multivariable			Univariable		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Treatment	Surgery	Ref.			Ref.			Ref.			Ref.			Ref.		
	DCRT	1.344	0.407–1.361	0.338	1.054	0.601–1.851	0.854	0.440	0.903–5.729	0.081	0.901	0.337–3.653	0.864	1.441	0.966–2.149	0.074
Age	≤60 years	Ref.			Ref.			Ref.						Ref.		
	>60 years	2.274	1.329–3.891	0.078	1.860	1.164–2.970	**0.009**	1.236	0.663–2.302	0.505				1.185	0.805–1.746	0.389
Gender	Male	Ref.			Ref.			Ref.						Ref.		
	Female	1.676	0.669–4.201	0.270	1.153	0.466–2.854	0.758	0.692	0.168–2.846	0.610				0.818	0.360–1.857	0.631
Location	Cervical-upper	Ref.			Ref.			Ref.			Ref.			Ref.		
	Middle	0.887	0.425–1.850	0.748	1.051	0.546–2.022	0.881	0.920	0.424–2.200	0.938	0.702	0.315–1.564	0.387	0.695	0.442–1.091	0.114
	Lower	0.534	0.231–1.234	0.142	0.585	0.278–1.230	0.157	0.462	0.186–1.149	0.097	0.365	0.144–0.928	0.034	0.679	0.416–1.107	0.121
ECOG PS	0	Ref.			Ref.			Ref.						Ref.		
	1–2	1.469	0.850–2.539	0.169	1.416	0.887–2.262	0.145	1.521	0.851–2.718	0.157				1.708	0.753–3.877	0.200
CCI	0–2	Ref.			Ref.			Ref.			Ref.			Ref.		
	≥3	1.422	0.736–2.748	0.294	0.935	0.495–1.770	0.839	0.426	0.057–0.967	**0.045**	0.234	0.039–1.401	0.112	1.275	0.798–2.037	0.309

Abbreviations: DCRT, definitive chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; PS, performance status; CCI, Charlson Comorbidity Index; HR, hazard ratio; CI, confidence interval; Ref, reference.

Endoscopic resection (ER) on failure patterns

To investigate the impact of ER conducted before DCRT on failure patterns, we divided the DCRT group into two subgroups: patients who received ER before DCRT (ER group) and those who received DCRT alone (non-ER group). The ER group had a single case of locoregional recurrence, in contrast to the 14.8% recurrence rate in the non-ER group.

Discussion

Survival rates

Esophagectomy has been regarded as the standard of care for patients with cT1bN0M0 esophageal cancer, whereas DCRT is recommended for patients who are medically unfit for major surgery. In this study, we verified differences in patient characteristics between surgery and DCRT groups, as depicted in Table 1. Patients in the DCRT group were older than those in the surgery group by 9 years, displayed worse performance status, and had higher comorbidities. Despite such disadvantages, several studies have demonstrated an equivalent long-term survival rate of DCRT compared to that of surgery. In a prospective phase II trial (JCOG 9708), Japanese investigators evaluated the efficacy of DCRT in patients with stage I ESCC and reported a favorable outcome with a 4-year OS rate of 80.5% (15). In another prospective randomized controlled study (JCOG0502) that compared surgery and DCRT in early–stage ESCC, equivalent 5-year OS rates (86.5% and 85.5%, respectively) and high clinical response rate (87.3%) in the CRT arm were reported (15). Prospective randomized studies demonstrated that esophagectomy did not result in a higher survival rate in individuals who responded well to neoadjuvant CRT in the context of locally advanced tumors. Additionally, early-stage tumors have a greater likelihood of exhibiting a favorable response to CRT compared to locally advanced tumors. In the current study, we noted a very high clinical response rate (95.5%) after DCRT (Table 4). Moreover, the

aforementioned rate is a little higher than that reported in Japanese studies, The difference could be attributed to the possible variability in response evaluation methods of participating institutions and the retrospective nature of this study. However, we confirmed the equivalence of two treatments in DFS and OS despite marginal significance in OS rates (p = 0.072). This marginal difference could be explained as follows: First, poor patient characteristics in the DCRT group could have affected the survival rates. Second, salvage treatment could have increased the survival rate in the surgery group. As depicted in Table 6, local treatments with curative aim could be performed in about 60% of cases in the surgery group. In contrast, salvage esophagectomy or curative CCRT could be performed in less than 40% of the DCRT group. Although the exact reason for the marginal difference remains unknown, our results demonstrated that DCRT could be an equivalent treatment to esophagectomy with regard to DFS and OS for cT1bN0M0 tumors.

Recurrence patterns

No difference was identified between the surgery and DCRT groups in locoregional recurrence rate as shown in figure 1A and 1B (12.0% and 14.8%). However, recurrence sites were not similar to each other as esophagus was the most common site of recurrence in the DCRT group, and regional lymph nodes were the major failure site in the surgery group. It is clear that esophageal recurrence was affected by the change in anatomic structures after esophagectomy. And the difference in nodal failure rates might be attributed by surgery but

we may explaine it in other ways. First, the high recurrence rate in the esophagus could have masked the subsequent regional failures in the DCRT group. But if we consider the equivalent LRDFS rates between the two groups, the possibility of the masking effect does not seem to be a significant factor. Second, DCRT was effective in eliminating microscopic tumors in the regional lymph nodes, especially those that were difficult to remove by esophagectomy. It seems to be probable but we do not recommend a routine use of wide radiation field for all cT1bN0M0 tumors as the most common recurrence site was identified to be the esophagus among DCRT patients, and wide field could increase unnecessary irradiation of mediastinal structures.

Salvage esophagectomy could be performed in 30% of DCRT patients with good performance status, implying that surgical resection could be reserved for salvage treatment in patients who are medically fit for major surgery when esophageal cancer is diagnosed. Another option for improving the local control rate is adopting ER in feasible cases. ER will remove the substantial portion of gross tumors, converting them into a microscopic disease that can be managed by CRT more successfully.

Role of ER before DCRT

Early-stage esophageal cancers such as Tis or T1a can be dissected successfully by endoscopic mucosal resection (EMR) or ESD and have been recommended by several

national guidelines. However, the role of EMR or ESD in cT1b is under investigation due to non-negligible risks of lymph node metastasis. Certain investigators have reported that ER followed by CRT can produce excellent local control and an equivalent survival rate to surgery in cT1bN0M0 ESCC. For instance, Yoshimizu et al. demonstrated a significant increase in the local control rate with the addition of ER before DCRT ($p < 0.05$) (16). Similarly, Kawaguchi et al. reported no local recurrence in the ER followed by the CRT group in contrast to 19.4% of the non-ER DCRT patients (17). Furthermore, Minashi et al. observed that endoscopic resection before DCRT improved the 3-year survival rate reaching levels comparable to those achieved with radical surgery (18), and demonstrated that improvement in the local control was related to increased survival rate. We similarly observed only one locoregional recurrence (in-field esophagus) among 15 patients with ER before DCRT, which was considerably lower than 12 locoregional recurrences in the non-ER group. However, we should be cautious in interpreting this result as these 15 patients may have had ER because, compared to non-ER group, their cT1b tumors were small, not circumferential, and shallow. Thus, it is very probable that tumors in the ER group were relatively in the early cT1b stage and a direct comparison between ER and non-ER groups produced biased results. However, the possible role of ER in removing radioresistant tumor cells that persist after DCRT, and cause tumor recurrence cannot be denied.

Accuracy of clinical evaluation for stages

As displayed in Table 5, the overall accuracy of predicting pT1bN0M0 by current evaluating methods was just 56%, and the other patients were either over- or under-estimated. Especially, the overestimation of pTis-T1aN0M0 occurred in 25.2% of patients and esophagectomy could have been avoided in these cT1bN0M0 patients if we can use more accurate diagnostic modalities in the future. Similarly, metastatic lymph nodes were not detected by EUS, CT, and FDG-PET scans in about 20% of patients. We believe similar over- or under-estimation of stages could occur in the DCRT group, but in these patients, the possibility of over- or under-treatment will be very low as the recommended radiation dose for esophageal cancer is not considerably variable according to stages. The presence of undetected lymph node metastasis, which was missed in the radiation field, does not appear to be a serious problem as only one out-of-field lymph node recurrence was observed in the DCRT group.

Complications

As patients with high ECOG and CCI status tend to undergo DCRT rather than surgery, toxicities are one of the major concerns both during and after the treatment. Serious cardiopulmonary toxicities were reported in the era of conventional radiotherapy (19). In our study, grade 3 cardiac toxicities were observed in only two patients (2.2%) who had underlying cardiopulmonary disease before the diagnosis of esophageal cancer. Grade 3 esophageal stenosis was observed in 2 patients (2.2%) and they were relieved by balloon

dilatation. However, we should consider the possibility that the incidence of toxicities could be potentially under-reported in this retrospective study. Therefore, we should attempt to reduce the radiation dose to the cardiopulmonary system, given that the majority of DCRT patients are old and present comorbidities. Advanced technologies, such as proton or carbon ion therapy are expected to reduce radiation induced toxicities.

This study had several limitations. First, this study was a retrospective analysis of the data from multi-institutions, and we cannot deny the possibility of biases in each institution. Second, variations existed in radiotherapy techniques such as the use of ENI according to each institutional protocol and each radiation oncologist's perspective. However, radiation fields and doses were generally acceptable. Third, ER patients could have relatively smaller and shallower tumors compared to non-ER patients as ER is not usually attempted for deep and extensive T1b tumors. Despite limitations, the unique strength of this study is that it is one of the largest cohort studies on patients with cT1bN0M0 ESCC, which compared esophagectomy and DCRT. Materials were accumulated from leading cancer centers in Korea, and their treatment qualities were accredited by the Korean Society of Radiation Oncology. All analyses were performed logically and rationally to reach non-biased, and reliable results. As early-stage esophageal cancers are increasingly being diagnosed through annual health screening, we expect that more patients can be cured with their organs preserved and high quality of life maintained.

Summary

In this retrospective multi-institutional study, we compared DCRT and radical esophagectomy in patients clinically diagnosed with T1bN0M0 ESCC. Both treatments were equivalent to each other in OS, LRDFS, and DFS rates. Considering the advanced age, and grades of CCI and ECOG in comparison to the surgery group, DCRT emerges as a safe and comparable alternative to surgery without serious complications.

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국문요약

목적: 임상적 **T1b**N0M0 식도 편평 세포 암종환자에서 식도 절제술과 근치적 항암방사선요법간의 치료 결과를 조사하고자 하였다.

대상 및 방법: 2010 년 1 월부터 2020 년 4 월까지 국내 11 개의 기관에서 치료를 받은 cT1bN0M0 식도암으로 진단된 환자에 대해 후향적 분석을 시행하였다. 식도절제술과 DCRT 환자의 질병 재발 및 전제 생존율을 비교하였다.

결과: 식도절제술을 받은 총 333 명의 환자와 근치적 항암방사선요법을 받은 환자 88 명이 분석에 포함되었고, 수술군은 근치적 항암방사선요법군에 비해 나이가 젊고 수행능력도 더 좋았다. 근치적 항암방사선요법 군에서는 88 명(95.5%)의 환자들이 치료 한달후 시행한 반응 검사에서 임상적 완전 관해를 달성하였다. 중앙값 55 개월의 추적기간동안 질병재발은 수술군에서 64 명 (19.2%), 근치적 항암방사선요법군에서는 15 명 (17.0%)에서 발생하였다. 5 년 국소 및 림프절무진행 생존율은 수술군에서 86.0%, 근치적 항암방사선요법군에서는 75.4% 이었다 (p=0.336). 5 년 원격전이 무병생존율은 수술군과 근치적 항암방사선요법군에서 각각 84.5%, 92.9% 이었다 (p=0.073). 수술군에서 향상된 전체 생존율의 경향성을 보여 주었던 반면에 (77.8% vs. 65.8%, p = 0.072), 두 군간 무진행생존율에서 유의한 차이를 보이지 않았다 (78.5% vs. 74.7%, p = 0.854).

결론: 이 연구에서 근치적 항암방사선요법이 국소림프절무진행 생존율, 무진행생존율및 전체생존율에서 식도절제술과 동등함 보여주었다.

핵심 용어: 식도암, 근치적 항암방사선요법, 내시경점막하박리술, 근치 식도 절제술