

Efficacy of Endoscopic Resection and Selective Chemoradiotherapy for Stage I Esophageal Squamous Cell Carcinoma

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INTRODUCTION



- Recent endoscopic imaging technologies have enabled the early detection of esophageal squamous cell carcinoma (ESCC).
- ER has the advantage of being able to evaluate the actual depth of tumor invasion and the presence or absence of lymphovascular invasion (LVI) using the resected specimen. In addition, it has a local therapeutic effect by removing the primary tumor.

INTRODUCTION



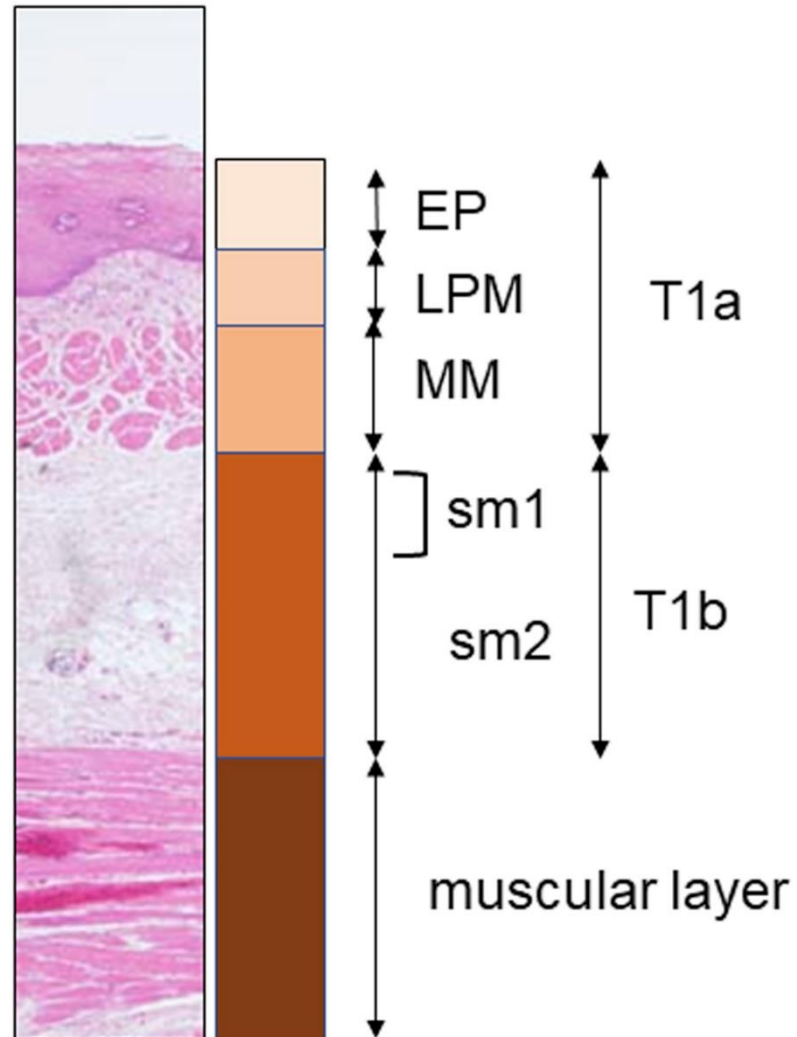
- Clinical stage I (T₁N₀M₀) ESCC can be treated with surgery, with a 5-year survival rate of 70%–80%.
- However, at times the pathologic diagnosis after surgical resection reveals mucosal (T_{1a}) cancer without lymph node metastasis, which indicates that some stage I ESCC patients have the potential to be treated using less-invasive procedures, such as ER alone.
- CRT is also a curative treatment option for stage I ESCC but local control was not good.

INTRODUCTION



- This raises new questions related to how early ESCC is managed because it can be treated with different therapeutic modalities, such as endoscopic resection (ER), surgical resection, and chemoradiotherapy (CRT).
- Aim of the study: evaluate the efficacy and safety of selective CRT based on diagnostic ER for clinical T1b (SM₁₋₂) ESCC.

Subclassification for superficial esophageal cancer by endoscopic resection



METHODS



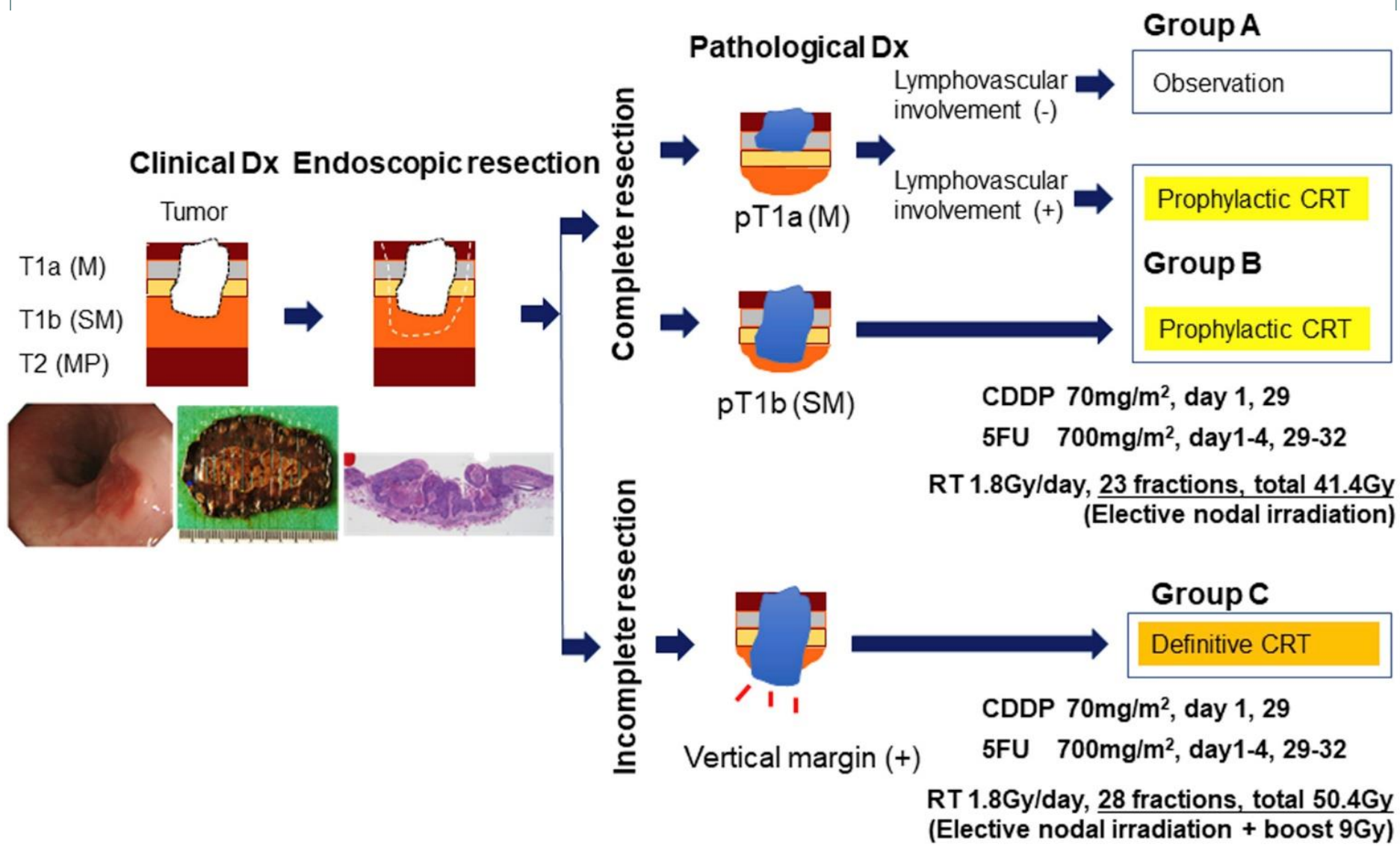
- Multi-institutional, prospective confirmatory study of 176 patients with stage I thoracic ESCC who underwent ER from December 2006 through July 2012.
- 23 institutions in Japan.

METHODS



Inclusion criteria:

- Age between 20 and 75 years
- Performance Status of 0 or 1
- Histologically proven SCC or basaloid cell carcinoma on biopsy
- Location within the thoracic esophagus
- Main tumor depth of invasion as cSM1–2 confirmed by EUS
- Stage cNo/Mo confirmed by CT scan
- Main tumor size ≤ 5 cm and circularity $\leq 3/4$
- Absence of ulcerative lesions in tumors
- Absence of synchronous cancer
- No previous treatment with CT/RT against any other malignancy
- No previous surgical treatment for esophageal cancer



METHODS



- Primary endpoint:
3-year overall survival in group B (prophylactic CRT).
- Secondary endpoints:
3-year overall survival for all patients to evaluate whether this step-up strategy is equivalent to surgery.
- If lower limits of 90% confidence intervals for the primary and key secondary end points exceeded the 80% threshold, the efficacy of combined ER and selective CRT was confirmed.
- Other secondary end points were progression-free survival, adverse events (AEs) of ER and CRT.

METHODS



Follow-up:

Every 4 months after ER for 3 years then at least every 6 months

- Physical examination
- Upper GI endoscopy
- CT scan of the neck, chest, and abdomen
- Tumor marker (SCC)

If the patient relapsed during the observation period, subsequent treatment, including salvage surgery or CT, could be decided by his or her physician.

RESULTS

Table 1. Patient and Lesion Characteristics

Characteristic	Data
Median age, y (IQR) (range)	63 (59–67) (42–75)
Sex, n	
Male	147
Female	30
ECOG Performance Status, n	
0	177
1	0
Histologic type, n	
SCC	177
Multiple lesions, n	
Yes	19
1 lesion/2 lesions	12/7
No	158
Tumor location, n	
Upper	16
Middle	120
Lower	41

RESULTS

Table 1. Patient and Lesion Characteristics

Characteristic	Data
Macroscopic type, n	
0-I	19
0-IIa	30
0-IIb	4
0-IIc	124
Clinical diagnosis of invasion, n	
SM1	114
SM2	63
Diameter of tumor, <i>cm</i> , median (IQR) (range)	2.5 (1.7–3.0) (0.5–5.0)
Circumference of tumor, n	
$\leq 1/4$	72
$> 1/4, \leq 1/2$	82
$> 1/2, \leq 3/4$	23

RESULTS

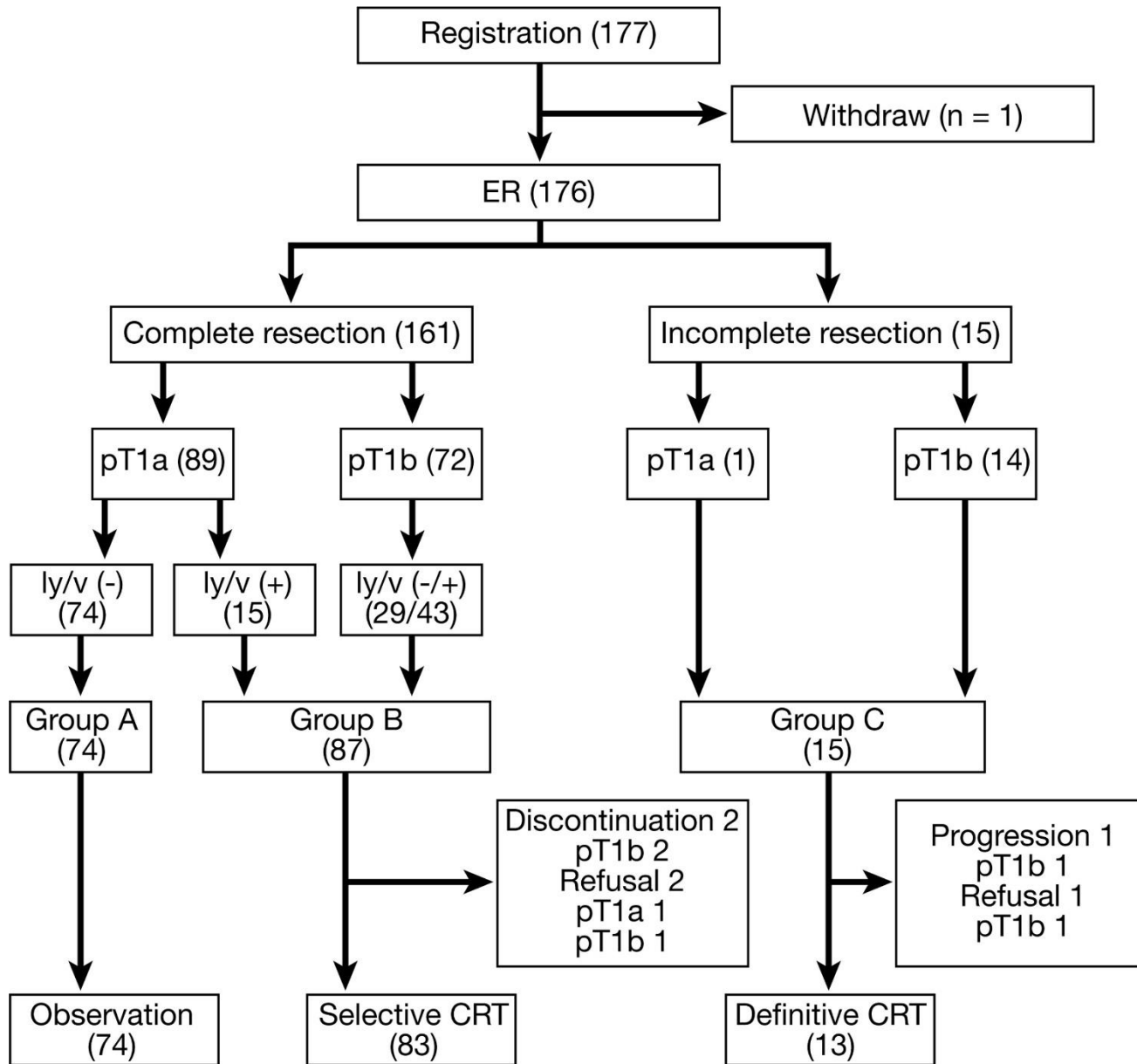
Table 2. Results of Endoscopic Resection for the Main Primary Tumor (n = 176)

Variable	Data
Method of ER, n	
EMR	35
ESD	141
Type of resection, n	
En bloc resection	161
Piecemeal resection	15
Diameter of mucosal defect, <i>cm</i> , median (IQR) (range)	4.0 (3.0–5.0) (1.0–11)
Circumference of mucosal defect, n	
$\leq 1/4$	23
$>1/4, \leq 1/2$	74
$>1/2, \leq 3/4$	59
$>3/4$	20

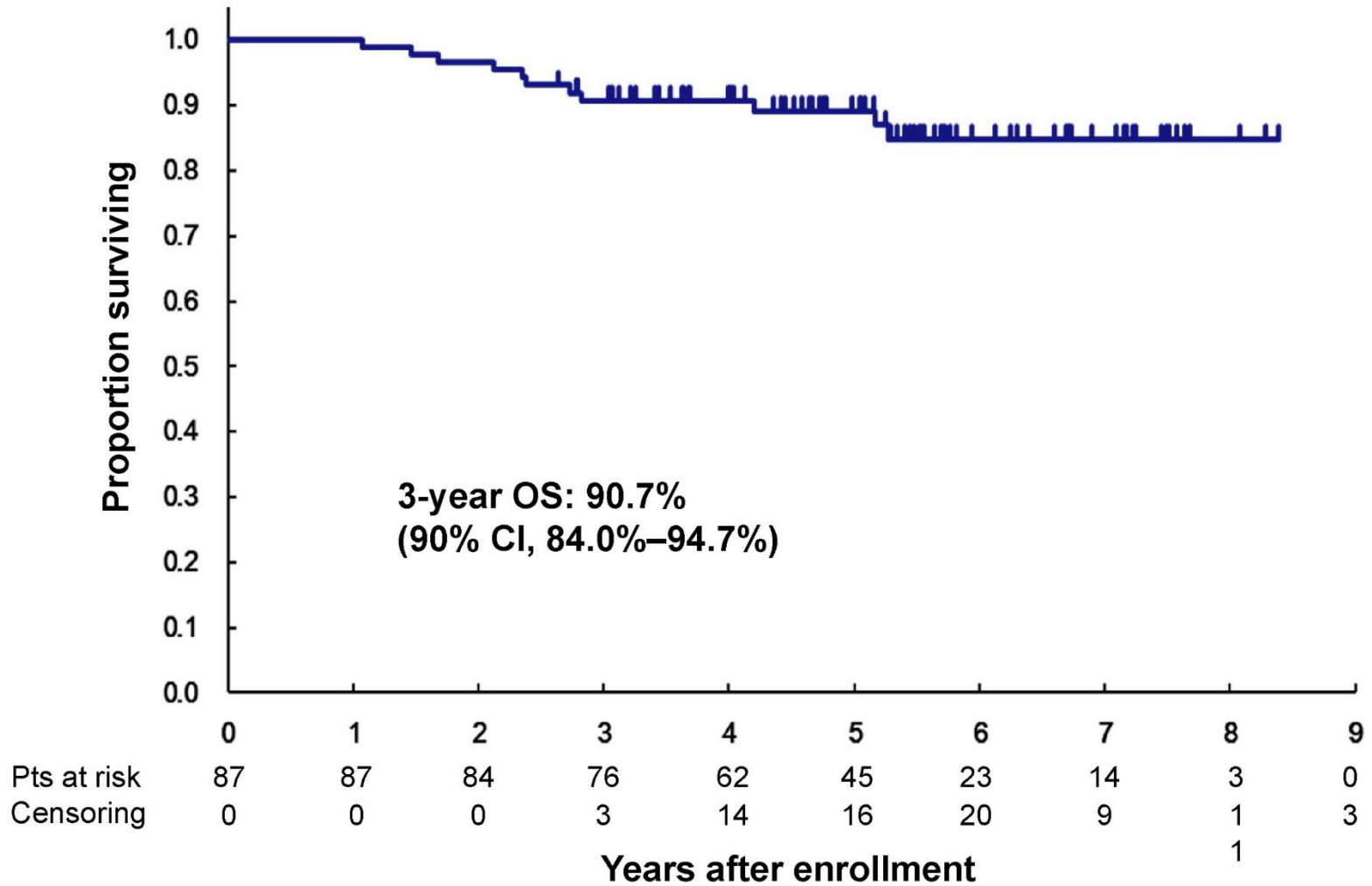
RESULTS

Table 2. Results of Endoscopic Resection for the Main Primary Tumor (n = 176)

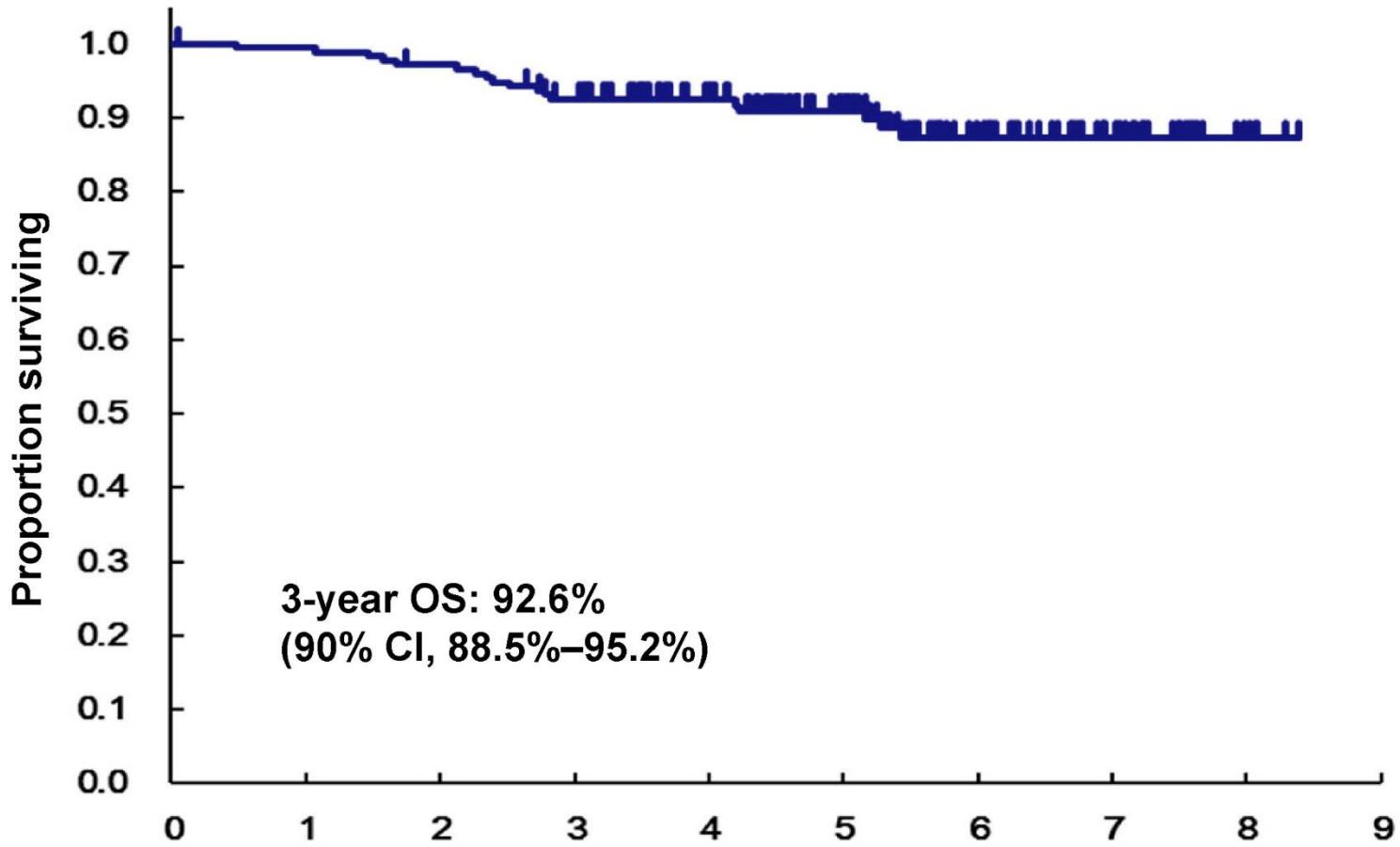
Variable	Data	
Pathologic invasion, n		
EP (M1)	3	T1a=90/176
LPM (M2)	31	
MM (M3)	56	
SM1	17	
SM2	69	
LVI, n		
Positive	68	
Negative	108	
Lateral resection margin, n		
Positive or uncertain	29	
Negative	147	
Vertical resection margin, n		
Positive or uncertain	15	
Negative	161	



Overall survival of patients with selective CRT (group B)



Overall survival of all enrolled patients



Pts at risk	177	175	170	157	127	92	47	25	5	0
Censoring	0	1	1	5	30	33	42	22	20	5

Years after enrollment

RESULTS



- Metastatic recurrence was observed in 15 (8.5%) of all the enrolled patients:
 - 1 in group A
 - 10 in group B
 - and 4 in group C
- The recurrence sites were cervical, thoracic, and abdominal lymph nodes.
- Organ metastasis appeared in 5 patients (2 in the liver, 2 in the lungs, 1 in the pleura and 1 in the bone).

RESULTS



- 7 patients with recurrent cancer in only the lymph nodes underwent salvage surgery, and 2 were alive at the final follow-up.
- 3 (1.7%) patients had local recurrence, 2 of which were resectable using local treatment, including ER.
- The 3-year progression-free survival rate for all of the enrolled patients was 89.7%, which did not include the recurrence that could be treated with curative resection.

RESULTS



18 patients died during the study period up to the cutoff date:

- 11 died of esophageal cancer (1 in group A, 7 in group B and 3 in group C).
- 5 died of other causes (brain hemorrhage, bile duct cancer, acute pancreatitis, and pneumonia).
- 2 died of unknown causes.

RESULTS



Table 3. Adverse Events Associated With Endoscopic Resection and Chemoradiotherapy

Variable	Grade 1, n	Grade 2, n	Grade 3, n	Grade 4, n	Grade 3-4, %
AEs associated with ER					
Intraoperative					
Hypoxia	—	1	0	0	0
Perforation, esophagus	0	2	0	0	0
Hemorrhage/bleeding associated with surgery	—	—	0	0	0
Intraoperative injury, esophagus	3	0	0	0	0
From the end of ER to discharge					
Fever	17	1	0	0	0
Heartburn	13	1	0	-	0
Pain, esophagus	60	8	0	0	0
Hemorrhage/bleeding associated with surgery	—	—	0	0	0
From discharge to CRT start					
Stricture/stenosis, esophagus	16	18	1	0	0.6

RESULTS



Table 3. Adverse Events Associated With Endoscopic Resection and Chemoradiotherapy

Variable	Grade 1, n	Grade 2, n	Grade 3, n	Grade 4, n	Grade 3–4, %
AEs associated with CRT					
Acute AEs					
Neutrophils	29	37	22	0	22.9
Hemoglobin	19	9	1	0	1.0
Platelets	27	7	4	0	4.2
Creatinine	30	3	0	0	0
Hyponatremia	47	-	7	0	7.3
Fever	8	2	0	0	0
Esophagitis	29	21	4	0	4.2
Dysphagia	23	11	2	0	2.1
Anorexia	27	26	7	0	7.3
Nausea	27	14	2	0	2.1
Mucositis/stomatitis	17	4	1	0	1.0
Pain, esophagus	17	8	1	0	1.0
Infection with grade 3 or 4 neutrophils	—	0	1	0	1.0
Late AEs					
Cardiac ischemia/ infarction	0	1	1	1	2.1
Pericardial effusion (non-malignant)	5	—	0	0	0
Pneumonitis	26	3	1	0	1
Pleural effusion (non-malignant)	5	2	0	0	0

DISCUSSION



- The current study showed that the new treatment strategy of selective CRT based on histologic evaluation using diagnostic ER provided survival rates comparable to those of surgery.
- In addition, the 3-year overall survival among all the enrolled patients was equal to that of surgery.
- Therefore, the nonsurgical treatment strategy of CRT selection based on a diagnostic ER should be considered for standard minimally invasive treatment.



- Clinically, it is recommended that the majority of patients with ESCC that is suspected to have invaded the submucosa undergo surgery, even those without lymph node metastasis.
- About one-half of the patients with clinical T1b (SM1–2) ESCC were diagnosed with pT1a ESCC in this study.
- For these patients, surgery might be an overly aggressive curative treatment, and ER can be the first choice for treatment to preserve the organ.

DISCUSSION



- Accurate discrimination of tumor invasion into the submucosa vs into the mucosa has been clinically challenging.
- Compared to surgery, ER is evidently less invasive, therefore, this line of treatment should be considered first.
- It is also as a tool for the histologic evaluation of tumor invasion, which can help advise and allow for the selection of the next appropriate treatment in ESCC patients.

DISCUSSION



- Selective CRT after ER has several merits over definitive CRT.
- First, complete removal of the primary tumor might reduce local failure after CRT.
- Second, the irradiation boost dosage to the primary site can be reduced, with an expected decrease in radiation-related AEs.

DISCUSSION



- The safety of diagnostic ER and selective CRT was clinically acceptable because no severe AEs were observed from these treatments in this study.
- Only 1 patient developed grade 3 esophageal stenosis, which was a possible risk from ER because a mucosal defect more than three-fourths of the circumference of the resected area after ESD potentially develops stenosis.

DISCUSSION



Limitations:

- No randomized controlled study and survival rates were not directly compared with those of surgery.
- The surgical studies included all T1b (SM1–3) ESCC patients, while this study included only patients with shallow T1b (SM1–2) ESCCs.



THANK YOU