

90073\_Auto\_Edited.docx

**Name of Journal:** *World Journal of Gastrointestinal Endoscopy*

**Manuscript NO:** 90073

**Manuscript Type:** ORIGINAL ARTICLE

*Retrospective Study*

**Comparative efficacy and safety between endoscopic submucosal dissection, surgery and definitive chemoradiotherapy in patients with cT1N0M0 esophageal cancer**

Shu-Ai Luo, Yu-Ying Sun, Ya-Ting Zeng, Chun-Yu Huang

**Abstract**

**BACKGROUND**

Endoscopic submucosal dissection (ESD) and surgical resection are the standard of care for cT1N0M0 esophageal cancer (EC), whereas definitive chemoradiotherapy (d-CRT) is a treatment option. Nevertheless, the comparative efficiency and safety of ESD, surgery and d-CRT for cT1N0M0 EC remain unclear.

**AIM**

To compare the efficiency and safety of Endoscopic submucosal dissection (ESD), surgery and definitive chemoradiotherapy (d-CRT) for cT1N0M0 EC.

**METHODS**

We retrospectively analyzed the hospitalized data of a total of 472 consecutive patients with cT1N0M0 EC treated at Sun Yat-sen University Cancer center between 2017-2019 and followed up until October 30th, 2022. We analyzed demographic, medical recorded, histopathologic characteristics, imaging and endoscopic, and follow-up data. The Kaplan-Meier method and Cox proportional hazards modeling were used to analyse the difference of survival outcome by treatments. Inverse probability of treatment weighting (IPTW) was used to minimize potential confounding factors.

## RESULTS

We retrospectively analyzed patients who underwent ESD ( $n = 99$ ) or surgery ( $n = 220$ ) or d-CRT ( $n = 16$ ) at the Sun Yat-sen University Cancer Center from 2017 to 2019. The median follow-up time for the ESD group, the surgery group, and the d-CRT group was 42.0 months (95%CI 35.0-60.2), 45.0 months (95%CI 34.0-61.75) and 32.5 months (95%CI 28.3-40.0), respectively. After adjusting for background factors using IPTW, the highest 3-year Overall survival (OS) rate and 3-year Recurrence Free Survival (RFS) rate were observed in the ESD group (3-year OS: 99.7% and 94.7% and 79.1%; and 3-year RFS: 98.3%, 87.4% and 79.1%, in the ESD, surgical, and d-CRT groups, respectively). There was no difference of severe complications occurred between the three groups ( $P \geq 0.05$ ). Multivariate analysis showed that treatment method, histology and depth of infiltration were independently associated with OS and RFS.

## CONCLUSION

For cT1N0M0 EC, ESD had better long-term survival and lower hospitalization costs than those who underwent d-CRT and surgery, with similar rate of severe complications occurred.

## INTRODUCTION

Esophageal cancer (EC) is an aggressive and poorly prognostic gastrointestinal tumor and one of the common causes of cancer death [1]. Over the past few decades, the proportion of patients with cT1N0M0 EC has increased due to improvements in endoscopic techniques and increased awareness of disease prevention. Approximately 90% of EC are squamous cell carcinoma (SCC) and vary by geographical region, with SCC being more common in Central Asia and China [2]. According to the depth of infiltration, cT1N0M0 EC is classified as mucosal carcinoma (T1a) and submucosal carcinoma (T1b), regardless of lymph node status.

<sup>2</sup> In the European Society of Endoscientific Oncology and the National Comprehensive Cancer Network guidelines, endoscopic resection is recommended for mucosal (T1a) lesions, surgical resection is recommended for patients with submucosal (T1b) lesions, and d-CRT is recommended for patients who are unable or unwilling to undergo surgery<sup>[3-4]</sup>. Endoscopic resection can accurately stage the patients, reduce the surgical complications, and achieve the effect of curative resection<sup>[5-7]</sup>, but carries a higher risk of recurrence (especially for large lesions). And radical esophagectomy is usually associated with postoperative complications, including anastomotic fistula, vocal cord paralysis, and pneumonia<sup>[8]</sup>.

<sup>2</sup> d-CRT is the standard treatment for patients with locally unresectable ESCC and an alternative treatment option for locally resectable ESCC<sup>[9-13]</sup>. However, in clinical practice, d-CRT is often selected as an alternative therapy for cT1N0M0 EC patients, depending on the comorbidities, tumor localization, and widespread expansion. Few reports have described the use of d-CRT in patients with stage I ESCC. A parallel group controlled trial conducted in Japan found that the survival of CRT in cT1bN0M0 ESCC was comparable to surgery and had acceptable toxicity<sup>[14]</sup>. However, the trial was conducted in Japan, and it was not clear about the generalizability of the evidence to different countries, while elderly patients and those not medically fit for surgery were excluded or underrepresented in the trial, and the study mainly included thoracic EC, thus questioning the generalizability of the results. Given the lack of sufficient evidence for the comparative efficacy of different treatments in cT1N0M0 EC, especially the role of d-CRT, we conducted this first retrospective study to compare the efficacy and complications of ESD, surgery and d-CRT.

## **MATERIALS AND METHODS**

### **Patient selection**

We retrospectively analyzed patients with cT1N0M0 EC treated with ESD, surgery and d-CRT between January 2017 and December 2019 at the Cancer Center of Sun Yat-sen University. The inclusion criteria were as follows:

- (1) All patients met the diagnostic criteria for cT1N0M0 EC: the tumor tissue was limited to the esophageal mucosa or submucosa without lymph node or distant metastasis (cT1N0M0), and the diagnosis was made by endoscopy, pathological biopsy and imaging evaluation.
- (2) Patients with histology of squamous cell carcinoma or precancerous lesions.
- (3) Patients without other concomitant malignancies.
- (4) Patients with complete clinical medical records.

The study was performed in accordance with the guidelines of the Declaration of Helsinki and was approved by the institutional review board of the Sun Yat-sen university cancer center.

### **Preoperative and postoperative evaluation**

The preoperative and postoperative evaluations mainly included endoscopic, imaging and histopathological examinations. Endoscopic examinations were performed by physicians with more than 6 years of endoscopic experience in the Department of Endoscopy of Sun Yat-sen University Cancer Center. Endoscopic examinations generally included conventional endoscopy with white light imaging (WLI) for all lesions; magnifying endoscopy with narrow-band or blue laser imaging (ME-NBI/BLI) using a GIF-H260Z (Olympus Corporation, Tokyo, Japan) or EG-L590ZW gastroscope (Fujifilm Corporation, Tokyo, Japan) for suspicious lesions; ultrasound endoscopy utilizing 7.5 MHz, 10 MHz, or 12 MHz radical scanning probes (SU 9000, EG-530UR2, Fujifilm; EU-ME2, Olympus) or a 20-MHz miniature probe (UM-DP20-25R, Olympus) was applied for identifying the depth of tumor infiltration or metastasis of lymph nodes. Preoperative enhanced CT, MR or PET-CT were performed to assist in the diagnosis of esophageal carcinoma. Postoperative follow-up examinations were started 1-2 months after the end of treatment, once every 3 months during the initial 2 years, once every 6 months from 2 to 5 years, and once a year after 5 years. R0 resection was defined as complete resection of the tumor, and histopathology showed a negative resection margin and no tumor residue after ESD or surgery therapy. Complete

response (CR) was defined as the disappearance of the primary tumor and the absence of irregular erosive lesions, ulcerative lesions, or apparently elevated lesions as observed during endoscopy and/or the absence of malignant cells in biopsy specimens after d-CRT therapy [15].

### **ESD, Surgery and d-CRT**

ESD was performed by endoscopists with extensive experience. All inpatients were placed in the left lateral position with general anesthesia under tracheal intubation. The esophageal lesion was stained with Lugol solution, and the resection margin was marked with APC or high-frequency electrocoagulation. A mixed liquid (0.9% NS:sodium hyaluronate = 4:1) was injected into the submucosa, the submucosa was dissected on the surface of the intrinsic muscular layer after circumferential incision outside the marked points, and the lesion was completely excised. Finally, the specimen was laid flat, fixed on a cork board with pins, soaked in formalin and sent for pathological examination. The intrinsic muscular layer of the esophagus was carefully examined endoscopically for any additional damage or residual tumor at the resection margin. The decision to add other additional treatments was made after a thorough evaluation based on the pathological findings and the therapeutic wishes of the patient and their family. In this study, two patients underwent radical esophageal cancer resection after ESD because of the positive resection margin of the pathological specimen.

Surgery was performed by experienced surgeons in our hospital. After general anesthesia was stabilized, the patients were placed in a supine position. After routine disinfection, surgeons removed the esophageal tumors, dissected the peripheral lymph nodes *via* thoracotomy or thoracoscopy and reconstructed the digestive tract using a laparotomy or laparoscopic approach. In this study, the pathological examination of one patient after esophagectomy indicated that tumor cells were visible at the resection margin of the specimen, so an extended surgical procedure was implemented.



The d-CRT regimen was discussed and decided by physicians with extensive experience in the medical oncology and radiotherapy departments of our hospital. d-CRT consisted of 5 courses of albumin paclitaxel (45~60 mg/m<sup>2</sup>) and cisplatin (20-25 mg/m<sup>2</sup>) on Day 1 every week along with concurrent radiotherapy by the intensity-modulated radiotherapy technique (IMRT). Radiation therapy was delivered using megavoltage equipment ( $\geq 6$  MV). The patients were treated 5 days per week at 1.8 to 2.0 Gy/d for a total dose of 60 Gy. The target volume of radiotherapy was individualized according to the primary tumor site and metastasis. The clinical target volume (CTV) of mid-thoracic esophageal cancer was defined as the gross tumor volume (GTV) with a 3 cm margin for upper and lower extents and the lymph node target volume (GTV-nd) with a 0.5 to 1 cm margin for three-dimensional extents. The planned target volume was decided according to the actual positional error and was generally formed by a 0.5 cm margin for three-dimensional outward extents based on CTV and a 0.3 cm margin for cervical or upper thoracic esophageal cancer fixed by head, neck and shoulder mesh.

### Statistical analysis

The statistical methods used in this study included Student's *t* test (or Mann-Whitney U test) and Fisher's exact test (or Pearson's chi-square test). The mean  $\pm$  standard deviation (mean  $\pm$  SD) for normally distributed measures was expressed by *t* test and the median and interquartile range [M (P25,P75)] for nonnormally distributed measures were expressed by rank sum test; the count data were expressed as percentages (%) and compared by chi-square test ( $\chi^2$  test). To account for selection bias and potential confounding factors between groups in comparisons of outcome, we performed weighted propensity score analysis to control for differences in baseline characteristics between patients underwent ESD, surgery and d-CRT. The propensity model was generated using the inverse probability treatment weighted (IPTW) method. Each patient was weighted by inverse probability with the goal of balancing observable features. The Bonferroni correction was needed as a conservative method for probability

thresholding to control the occurrence of false positives. 3-year OS and RFS were calculated and expressed as months. OS was right censored if the patient was alive at study termination or was lost to follow-up, and patient death was considered an event. In RFS analysis, the recurrence of EC after eradication therapy was considered an event. The follow-up period was calculated from treatment, and the cutoff date was October 30th, 2022. Follow-up ended when patients died or were lost to follow-up and cause of death and cause of loss analysis was analyzed. Time to recurrence was calculated from the time of treatment to the time of the most recent endoscopic evaluation at our facility or another hospital. The survival curves were plotted using the Kaplan-Meier method, and OS and RFS rates of therapeutic groups were compared by log-rank test. Cox proportional hazards modeling was used to assess the hazard ratios (HRs) and 95% confidence intervals (CIs). All data were analyzed by SPSS version 25.0 and R version 4.3.1. All tests were two-sided with a significance level of  $P < 0.05$ .

## RESULTS

### Patient characteristics and complications

A total of 3911 patients with EC were treated in our hospital between January 2017 and December 2019, including 75 patients with precancerous esophageal lesions and 472 patients with cT1N0M0 EC. After exclusion, we retrospectively analyzed cT1N0M0 EC patients who underwent ESD ( $n = 99$ ) or surgery ( $n = 220$ ) or d-CRT ( $n = 16$ ) at our hospital. Table 1 and 2 show the baseline characteristics and complications of patients in the ESD, surgery and d-CRT groups before and after IPTW adjustment.

Before IPTW adjustment, patients in the d-CRT group were older than those in the ESD and surgery groups. In the d-CRT group, there were 6 patients with clinical stage T1a (cT1a: M1-2), of whom 4 (66.7%) achieved CR, and 10 patients with clinical stage T1b (cT1b: M3-SM1-3), of whom 8 (80.0%) achieved CR. Among the cT1a patients, an 87-year-old patient developed more serious radiotherapy toxic side effects such as radiation pneumonia and finally died despite achieving CR, while one patient who did not achieve CR died of esophageal cancer and severe complications of radiotherapy.



Among the cT1b patients, severe complications were observed in four patients who achieved CR and survived, including three patients with esophageal stricture and two patients with radiation pneumonia. In contrast, one patient who did not achieve CR died after receiving additional treatments because of lymph node metastasis. Patients in the surgery and d-CRT groups had more complications than those in the ESD group. Esophageal stricture was the main postoperative complication (surgery vs. ESD vs. d-CRT: 17.7% vs. 4.1% vs. 18.8%,  $P = 0.004$ ).

While after IPTW adjustment, the covariate balance in the three groups was improved; the number of background factors with P-value above 0.05 was increased from 1 to 7. Complication rates were similar in the three groups, with all P-values > 0.05.

### **Hospitalization costs and follow-up**

Table 3 shows the hospitalization costs and remedies after recurrence or metastasis in the ESD, surgery and d-CRT groups. The median follow-up time was 42.0 months (95%CI 35.0-60.2) in the ESD group, 45.0 months (95%CI 34.0-61.75) in the surgery group and 32.5 months (95%CI 28.3-40.0) in the d-CRT group. The ESD group had the lowest hospitalization costs, while the d-CRT group had the highest hospitalization costs among the three groups. One patient died of esophageal cancer in the ESD group. In the surgery group, sixteen patients died of progression or metastasis of esophageal cancer (84.2%), two patients died of postoperative multiorgan failure, and one patient died of severe respiratory disease. Two patients died of esophageal cancer, and one patient died of severe complications of radiation therapy in the d-CRT group. During the follow-up period, four patients developed recurrence or metastasis (4.0%), and three patients underwent surgical resection of the lesions in the ESD group, while thirty-eight patients in the surgery group developed recurrence or metastasis (17.3%), and thirty-one patients underwent salvage treatments. Additionally, one patient in the d-CRT group was treated with palliative chemoradiotherapy after recurrence or multiple metastases.

### **Survival analysis**

To compare 3-year OS and RFS in the ESD, surgery and d-CRT groups, the survival analysis was performed with IPTW adjustment and using Bonferroni correction to control the occurrence of false positives. Figure 1 shows the Kaplan-Meier survival curves before and after IPTW adjustment. The 3-year OS and RFS of ESD were superior to those of surgery and d-CRT (OS: ESD: 99.7%, Surgery: 94.7%, d-CRT: 79.1%; RFS: ESD 98.3%, Surgery: 87.4%, d-CRT: 79.1%).

We further investigated the risk factors for OS and RFS in the different treatment modalities. Figure 2 shows the results of the Cox proportional hazards model for OS and RFS after IPTW adjustment. Multivariate analysis showed that treatment method, histology and depth of infiltration were independently associated with OS and RFS.

### **DISCUSSION**

Many studies have compared the outcomes of ESD and surgery, or surgery and CRT in the treatment of cT1N0M0 EC, but there is a lack of studies directly comparing the efficacy and safety between ESD, surgery and d-CRT. After analyzing our included patients' clinical data before and after IPTW adjustment, we found that ESD yield better OS, RFS rates and lower hospitalized costs than surgery and d-CRT. Multivariate analysis showed that treatment method, histology and depth of infiltration were independently associated with OS and RFS, and it was similar to the previous study [16].

We explored the reasons for the difference in 3-year OS and RFS between the three treatments. We found that the depth of infiltration was more superficial in patients in the ESD group and that the local oncological control rate with ESD or surgery was higher, so patients could achieve tumor-free status to a greater extent. Patients in the d-CRT group were generally older and had high-grade and larger tumors, so EC was more likely to progress to an advanced stage and could not achieve CR. Our study showed that the rates of CR and severe complications for patients who received d-CRT were 75.0% and 43.8%, respectively, a relatively lower curative rate and higher

complication rate than ESD and surgery. Those factors were perhaps associated with the significant difference in 3-year OS and RFS between the ESD, surgery and d-CRT groups.

Besides, the severe complications were similar among patients treated by these therapy. But we found that esophageal stricture was the major complication of the three treatment methods. Several previous studies have shown that the circumferential extent of the tumor and infiltration depth were independent risk factors for esophageal stricture [17-19]. Currently, clinical measures for the prevention and treatment of postoperative esophageal stenosis include esophageal dilatation, esophageal stent placement, mucosal injection or oral steroid hormone [20-22]. Meanwhile, some novel techniques are being investigated by other scholars [23-24]. However, the effectiveness of these methods requires more clinical evidence and there is no ideal therapy in current clinical practice, so we are also conducting relevant research on this aspect.

By comparing the efficiency and complication rate between ESD, surgery and d-CRT, we summarize the experience of our center: for early esophageal cancer with infiltration to M1 or M2, no lymph node metastasis, no distant metastasis, and circumferential extent of tumor  $< 3/4$ , ESD was the preferred therapy. In particular, for patients with cervical or upper thoracic esophageal carcinoma, ESD is better than surgery. d-CRT should be attempted for patients who are of advanced age, frail, contraindicated to surgery and have an upper and circumferential extent of  $\geq 3/4$ .

In this study, we firstly conducted a retrospective study with a large sample size to compare the efficacy of early esophageal cancer treated with ESD, surgery and d-CRT, providing some useful suggestions. However, there are some limitations in our study. First, the sample size of our study was still not large enough, especially because the number of patients in the d-CRT group was insufficient. Second, the study was a single-center retrospective study, which has considerable limitations. Last, the data were obtained mainly from the medical records and follow-up, so there was a certain rate of missing visits and missing data. Therefore, multicenter prospective studies with larger

sample sizes or randomized controlled studies are needed to supplement the evidence of our study.

## **CONCLUSION**

This is a first retrospective study to compare OS, RFS and complications of ESD, surgery and d-CRT. In this study, we found that ESD attained better survival benefits and lower hospitalization costs than surgery and d-CRT, and they had similar complications rates. This study provides a more comprehensive analysis of the efficacy and safety of current cT1N0M0 EC treatment patterns and provides new evidence for the use of ESD in cT1N0M0 EC.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

For cT1N0M0 EC, the current study has mainly focused on surgery and ESD, while d-CRT is a complementary treatment for cT1N0M0 EC. Studies on estimating the therapeutic effect and safety of d-CRT, surgery and ESD are not sufficient, so this study is important.

### ***Research motivation***

Early-stage esophageal cancer is currently increasing year by year, and its treatment methods are also changing rapidly. It is very important to choose the treatment methods with good prognosis and fewer complications, while some patients have the dilemma of treatment choice due to age, cost and other reasons. It is very important to summarize and compare the advantages and disadvantages of the existing treatment methods, which is very important for the health management of patients with esophageal cancer.

### ***Research objectives***

By comparing the efficiency and safety of Endoscopic submucosal dissection (ESD), surgery and definitive chemoradiotherapy (d-CRT) for cT1N0M0 EC, to provide a clinical basis for the treatment selection of cT1N0M0 EC and to achieve better prognosis and quality of survival for EC.

### ***Research methods***

We retrospectively analyzed the medical records, pathology, imaging and endoscopic findings, and follow-up results of the cT1N0M0 EC, met the inclusion criteria and adjusted the effects of confounding factors using IPTW method to conduct survival analysis, COX proportional risk regression analysis, collect complications and costs, rescue measures after recurrence, and finally evaluate the efficacy and safety of cT1N0M0 EC patients receiving ESD, surgery and d-CRT.

### ***Research results***

Results showed that ESD had better survival outcomes, lower hospital costs and acceptable occurrence of complications. This study provides a more comprehensive analysis of the efficacy and safety of current cT1N0M0 EC treatment patterns and provides new evidence for the use of ESD in cT1N0M0 EC. <sup>8</sup> To our knowledge, our study is the first to compare the effects of three treatments for cT1N0M0 EC. In addition, there are relatively few studies on d-CRT for cT1N0M0 EC patients, and our study can provide relevant evidence of d-CRT for cT1N0M0 EC, so it has a certain innovation.

### ***Research conclusions***

This is a first retrospective study to compare overall survival (OS), recurrence free survival (RFS) and complication rate of ESD, surgery and d-CRT, and show that ESD attained better survival benefits and lower hospitalization costs than surgery and d-CRT, and they had similar complications rates. This study provides a more

comprehensive analysis of the efficacy and safety of current cT1N0M0 EC treatment patterns and provides new evidence for the use of ESD in cT1N0M0 EC.

*Research perspectives*

In the future, we will conduct subgroup analysis of survival outcomes for the three therapies in cT1N0M0 EC patients, and investigate methods to reduce the occurrence of complications.



# 14%

SIMILARITY INDEX

### PRIMARY SOURCES

- 1

[www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov)  
Internet

189 words — 5%
- 2

Ken Kato, Yoshinori Ito, Isao Nozaki, Hiroyuki Daiko et al. "Parallel-Group Controlled Trial of Surgery Versus Chemoradiotherapy in Patients With Stage I Esophageal Squamous Cell Carcinoma", Gastroenterology, 2021  
Crossref

147 words — 4%
- 3

[ascopubs.org](http://ascopubs.org)  
Internet

51 words — 1%
- 4

[bsdwebstorage.blob.core.windows.net](http://bsdwebstorage.blob.core.windows.net)  
Internet

49 words — 1%
- 5

Ken Kato, Yoshinori Ito, Isao Nozaki, Hiroyuki Daiko et al. "Parallel-group controlled trial of surgery versus chemoradiotherapy in patients with stage I esophageal squamous cell carcinoma", Gastroenterology, 2021  
Crossref

19 words — 1%
- 6

Ugo G. Falagario, Parita Ratnani, Anna Lantz, Ivan Jambor et al. "Staging Accuracy of Multiparametric Magnetic Resonance Imaging in Caucasian and African American Men Undergoing Radical Prostatectomy", Journal of Urology, 2020  
Crossref

19 words — 1%

- 
- 7 theses.ncl.ac.uk  
Internet 17 words — < 1%
- 
- 8 s3-eu-west-1.amazonaws.com  
Internet 14 words — < 1%
- 
- 9 www.4hfbiotec.com  
Internet 14 words — < 1%
- 
- 10 Dong-Fang Meng, Li-Sheng Zheng, Hai-Bo Zhang, Zi-Hao Liu, Yaru Tian, Ji Ma, Lei Fu. "Effect of First-line Chemotherapy Alone Versus First-line Chemotherapy Plus Radiotherapy on Survival in Patients with Locally Advanced Pancreatic Cancer in the IMRT era: A Retrospective Cohort Study", Research Square Platform LLC, 2023  
Crossref Posted Content 12 words — < 1%
- 
- 11 Haiyun Yang, Ming Xu, Xiufang Chi, Qun Yan, Yadong Wang, Wen Xu, Kangmin Zhuang, Aimin Li, Side Liu. "Higher PKD3 expression in hepatocellular carcinoma (HCC) tissues predicts poorer prognosis for HCC patients", Clinics and Research in Hepatology and Gastroenterology, 2017  
Crossref 12 words — < 1%
- 

EXCLUDE QUOTES ON  
EXCLUDE BIBLIOGRAPHY ON

EXCLUDE SOURCES OFF  
EXCLUDE MATCHES < 12 WORDS