# Efficacy and Prognosis of Chemoradiotherapy for 501 Patients With Postoperative Recurrence of Esophageal Cancer

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**Research**

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# Efficacy and prognosis of chemoradiotherapy for 501 patients with postoperative recurrence of esophageal cancer

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**Abstract**

**Background:** To analyze the efficacy and prognosis of chemoradiotherapy for patients with recurrence of esophageal cancer.

**Method:** A single center study was conducted in 501 patients with recurrent esophageal cancer who received chemotherapy and radiotherapy. Univariate or multivariate analysis was performed to assess the survival, recurrence pattern, prognosis of retreatment and influencing factors.

**Result:** The median time to recurrence of esophageal cancer was 11.6 months (range: 0.3-87.4 months), while the median survival time of chemoradiotherapy after recurrence was 12.1 months. Multivariate analysis identified gender, pN stage, log odds of positive lymph nodes (LODDS) value, chemotherapy cycle, recurrence time, and combined distant metastasis as independent prognostic factors ($P$=0.002, 0.035, 0.000, 0.000, 0.000, 0.001). In this study, 157 patients had combined combined distant metastasis, and the 1-, 3-, and 5-year survival rates of these patients after radiotherapy were 43.3%, 9.1%, and 5.5%, respectively. On the contrary, the 1-, 3-, and 5-year survival rates of patients with local regional recurrence (LRR) only were 53.6, 22.6%, and 16.4%, respectively. Statistically, the differences in the survival rates were significant between the above two groups of patients ($\chi^2$=10.786, $P$=0.001). Meanwhile, we identified recurrence time, chemotherapy cycle, and prescribed dose as the significant factors affecting the prognosis among 344 patients with postoperative LRR only ($\chi^2$=22.605, 13.957, 10.446; $P$=0.000, 0.000, 0.005).

**Conclusion:** This study showed that chemoradiotherapy is safe and effective in patients with recurrent esophageal cancer, while male patients with late pN stage, high LODDS, chemotherapy of ≤ 2 cycles, recurrence time of ≤ 24 months, or combined distant metastasis had a poor prognosis.

**Keywords:** Surgical treatment/recurrence, Recurrent therapy/radiotherapy, Recurrent therapy/chemotherapy, Prognosis

## Introduction

Cancer is the second leading cause of death in the world, and esophageal cancer is the sixth leading cause of cancer-related death, affecting more than 450000 people worldwide[1, 2]. In China, esophageal cancer is one of the common malignancies [3]. And there are mainly two types of esophageal cancer including squamous cell carcinoma and adenocarcinoma. The main treatment methods involve RT, surgery and chemotherapy. Surgical treatment is the main treatment mode for patients with esophageal cancer who can be surgically resected, but the clinical efficacy of radical resection remains unsatisfactory[4, 5]. The treatment failure can be mainly attributed to local regional recurrence (LRR) and combined distant metastasis in which LRR takes up 30% to 40% of the cases with 5-year survival rarely exceeding 25%[6, 7]. Once the treatment failure occurs, most patients have a poor prognosis and die within 1 year[8, 9]. At present, the main salvage treatment options for patients with postoperative recurrence include surgery, radiotherapy, chemotherapy, and chemoradiotherapy, while the curative effect is not ideal[10-12], and the optimal treatment regimen needs to be determined. Neoadjuvant radiotherapy and chemotherapy can improve the overall survival rate (OS) and local tumor control rate of patients, but neoadjuvant radiotherapy often increases the difficulties associated with surgery due to tissue edema and hemorrhage. Moreover, the patients in China usually choose surgery rather than chemoradiotherapy as their initial treatment option[13].

In addition, no consensus on radiotherapy target area, radiotherapy dose, and

85 combined chemotherapy regimens for patients with postoperative recurrence leads to
86 unsatisfactory outcomes of chemoradiotherapy [12, 14]. In this single center study, we
87 aimed to further clarify the efficacy of chemoradiotherapy for patients with recurrent
88 esophageal cancer and identify relevant prognostic factors.
89

90 **Materials and Methods**

91 A single-center study of 501 esophageal cancer patients was conducted. All patients
92 with a male to female ratio of 2.7:1 were admitted to the Fourth Hospital of Hebei
93 Medical University from January 2009 to December 2014. This study has been
94 approved by the Ethics Committee of Fourth Hospital of Hebei Medical University
95 (2020KY382) and all subjects participated in the study with a written informed consent.
96

97 **Inclusion and exclusion criteria**

98 The following inclusion criteria were used: (1) patients who received radical surgical
99 treatment for thoracic esophageal cancer, but did not have a history of neoadjuvant
100 treatment prior to the surgery; (2) definitely diagnosed as squamous cell carcinoma and
101 the absence of combined distant metastasis, as evidenced by postoperative pathological
102 examination; (3) patients who have not received adjuvant chemoradiation or
103 chemotherapy after surgery; (4) patients at first recurrence; (5) patients with karnofsky
104 score of ≥70; (6) complicated by multiple local/regional failures and/or combined
105 distant metastasis; (7) those who have no serious underlying diseases that affect

106 treatment and can tolerate chemoradiotherapy; and (8) no history of other complicated
107 malignancies.
108 The exclusion criteria were as follows: (1) patients who received preoperative
109 neoadjuvant therapy or postoperative adjuvant therapy; (2) diagnosed as non-squamous
110 cell carcinoma evidenced by postoperative pathology; (3) those who suffer from
111 underlying diseases that seriously affect treatment and cannot receive
112 chemoradiotherapy; (4) complicated by other malignancies; and (5) those who are
113 reluctant to receive adjuvant therapy or do not receive the therapy due to the doctor's
114 recommendations.
115
116 **Clinical and pathological data**
117 The median age at surgery was 59 years (range: 38-78 years), while the median age at
118 chemoradiotherapy for postoperative recurrence was 60.1 years (range: 38.8-81.9
119 years). Among all patients, 115, 24, and 25 had a history of hypertension, diabetes, and
120 coronary heart diseases, respectively. Notably, out of the above 164 cases, while 3
121 suffered from all the three types of diseases, 19 had any two of them. The median
122 esophageal length shown in barium meal angiography before operation was 5.0cm
123 (range: 1.0-15.0cm). Among all 501 patients, 431 (86.0%) underwent left thoracotomy,
124 while 26 (5.2%), 14 (2.8%), and 30 (6.0%) received right thoracotomy, cervical and
125 abdominal incisions, and three incisions of neck, chest and abdomen, respectively.
126 Based on degree of postoperative tissue differentiation, the patients were classified as

127 undifferentiated (40 cases), poorly differentiated (67 cases), moderately differentiated
128 (7 cases) and well differentiated (386 cases). Postoperative pathological examination
129 identified 37 cases with positive upper edge of the stump and 3 cases with positive
130 lower edge, while showing no case with any nerve invasion (Table 1).
131
132 **Log odds of metastatic lymph nodes**
133 Log odds of metastatic lymph nodes (LODDS) were calculated as follows:
134 LODDS=Log (number of positive lymph nodes + 0.5)/ (number of negative lymph
135 nodes + 0.5).
136
137 **Local/regional recurrence after treatment**
138 Local/regional recurrence after treatment mainly involves anastomoses and regional
139 lymph nodes. Anastomotic recurrence needs to be confirmed by electronic gastroscopy
140 bite pathological examination. For diagnosis of lymph node metastasis, needle biopsy
141 pathology was performed to confirm metastatic superficial lymph nodes, while CT,
142 MRI, PET/CT and/or B-ultrasound were conducted to diagnose lymph node metastasis
143 in the remaining areas. Regional lymph node metastasis involves lymph nodes located
144 in the supraclavicular area, mediastinum and abdominal cavity.
145
146 **Chemoradiotherapy**
147 All 501 patients received postoperative radiotherapy; among them, 362 patients

148 received intensity-modulated conformal radiotherapy, while the rest (139 patients)
149 underwent three-dimensional conformal radiotherapy. In the meantime, 181 and 320
150 patients received elective nodal irradiation (ENI) and involved-field irradiation (IFI),
151 respectively. The prescribed median dose was 60 Gy (range: 40-70 Gy). Out of 501
152 patients, 265 (52.9%) received a radiotherapy at a dose of 60 Gy.

153 Of 501 patients, 274 (54.7%) underwent chemotherapy that was concurrent
154 chemoradiotherapy. After radiotherapy, some patients continued to receive
155 consolidation chemotherapy. In this study, the median chemotherapy cycle was 3 (range:
156 1-7). And 168 patients received chemotherapy of ≥ 3 cycles.

157

158 **Follow up**

159 The follow-up mainly involved telephone follow-up and outpatient review, combined
160 with a review of case data. During the period from the operation date to December 31,
161 2019, the patients were reviewed every 3-6 months in the first year, and then every 6-
162 12 months thereafter. Of 501 patients, 36 (7.2%) were lost during the follow-up. We
163 counted the patients who were lost to follow-up as death cases on the date of the last
164 follow-up.

165

166 **Statistical Analysis**

167 SPSS 19.0 software was used to perform statistical analysis. Univariate survival
168 analysis and multivariate analysis were carried out by using Log-rank test and Kaplan-

169 Meier method, and Cox proportional hazards model, respectively. $P<0.05$ indicates that
170 the difference is statistically significant.
171
172 **Results**
173 **Postoperative recurrence**
174 The median postoperative recurrence time for all patients was 11.6 months (range: 0.3-
175 87.4 months). The recurrence occurred in the following sites: 84 cases (16.8%) with
176 simple supraclavicular lymph node recurrence, 254 cases (50.7%) with simple
177 mediastinal lymph node recurrence, 27 cases (5.4%) with simple anastomotic
178 recurrence, 28 cases (5.6%) with simple abdominal lymph node recurrence, 52 cases
179 (10.4%) with of the recurrence of supraclavicular and mediastinal lymph nodes, 10
180 cases (2.0%) with the recurrence of supraclavicular and abdominal lymph nodes, 4
181 cases (0.8%) with the recurrence of supraclavicular lymph nodes and anastomoses, 23
182 cases (4.6%) with the recurrence of mediastinal lymph nodes and anastomoses, 11 cases
183 (2.2%) with the recurrence of mediastinum and abdominal lymph nodes, 2 cases (0.4%)
184 with the recurrence of anastomoses and abdominal lymph nodes, 2 cases (0.4%) with
185 the recurrence of the lock, mediastinal and abdominal lymph nodes, and 4 cases (0.8%)
186 with the recurrence of the lock and mediastinal lymph nodes, and anastomoses.
187 We further reported 157 cases with distant metastases among all the patients. The
188 clinical study showed that out of 157 cases, 8 developed combined distant metastasis
189 earlier than recurrence, while combined distant metastasis and recurrence were detected

190 simultaneously in 6 patients. Statistically, the time for developing combined distant
191 metastasis was 5.4-94.4 months, and the median recurrence time was 27.3 months.
192
193 **Survival outcome**
194 The 1-, 3-, and 5-year survival rates of all postoperative patients were 88.8%, 43.8%,
195 and 27.3%, respectively, while the median survival time was 31.0 months. The 1-, 3-,
196 and 5-year survival rates of patients with radiotherapy following postoperative
197 recurrence were 50.3%, 18.1%, and 12.8%, respectively, and the median survival time
198 was 12.1 months.
199 The univariate analysis identified the following significant factors affecting the
200 prognosis: gender ($\chi^2$=11.427, *P*=0.001), smoking ($\chi^2$=7.385, *P*=0.007), drinking
201 ($\chi^2$=8.079, *P*=0.004), length of lesion in esophagography ($\chi^2$=7.140, *P* =0.008), pT
202 stage ($\chi^2$=9.607, *P* =0.022), pN stage ($\chi^2$=10.214, *P*=0.006), vascular tumor thrombus
203 ( $\chi^2$ =4.232, *P*=0.040), LODDS ( $\chi^2$ =25.233, *P*=0.000), chemotherapy cycles
204 ( $\chi^2$ =19.937, *P*=0.000), radiation dose ( $\chi^2$ =8.417, *P*=0.015), recurrence time
205 ( $\chi^2$ =25.616, *P*=0.000), and combined distant metastasis ( $\chi^2$ =10.786, *P*=0.001).
206 Conversely, there were no significant correlations between the prognosis and various
207 factors including age, underlying diseases, family history, location of the lesions,
208 method of thoracotomy, postoperative stump, number of dissected lymph nodes,
209 postoperative chemotherapy, irradiation method, and number of recurring areas (Table
210 1).

211 The multivariate analysis revealed a number of independent prognostic factors for
212 all patients such as gender (*P*=0.002), pN stage (*P*=0.035), LODDS (*P*=0.000),
213 chemotherapy cycles (*P*=0.000), recurrence time (*P* =0.000), and combined distant
214 metastasis (*P*=0.001) (Table 2).

215

216 **Table 2 Multivariate analysis of prognosis of patients with esophageal cancer**
217 **recurrence after radiotherapy (*n*=501)**

| Prognostic factors | B | SE | Wald | P | OB | 95%*CI* |
|---|---|---|---|---|---|---|
| **Sex** | -0.374 | 0.122 | 9.408 | 0.002 | 0.688 | 0.542-0.874 |
| **pN stage** | -0.222 | 0.106 | 4.435 | 0.035 | 0.801 | 0.651-0.985 |
| **LODDS** | 0.507 | 0.105 | 23.292 | 0.000 | 1.661 | 1.352-2.041 |
| **Chemotherapy cycle** | -0.488 | 0.113 | 18.587 | 0.000 | 0.614 | 0.492-0.766 |
| **Postoperative recurrence time** | -0.601 | 0.140 | 18.368 | 0.000 | 0.548 | 0.417-0.722 |
| **Combined distant metastasis** | 0.355 | 0.109 | 10.571 | 0.001 | 1.427 | 1.152-1.767 |

218

219 **Prognosis of postoperative patients with combined distant metastasis**

220 As shown in Fig. 1, a total of 157 patients developed combined combined distant
221 metastasis. The 1-, 3-, and 5-year survival rates of patients with combined distant
222 metastasis after radiotherapy were 43.3%, 9.1%, and 5.5%, respectively, and the median
223 survival time was 11.1 months. On the contrary, the 1-, 3-, and 5-year survival rates of
224 patients with LRR only after radiotherapy were 53.6, 22.6%, and 16.4%, respectively,
225 and the median survival time was 12.8 months. Statistically, the above differences were
226 significant ($\chi^2$=10.786, *P*=0.001).

227

228 **Prognosis of patients with only local recurrence after surgery**

229 A total of 344 patients had local recurrence. As shown in Table 3 and Fig. 2, the
230 subgroup univariate analysis identified postoperative recurrence time ($\chi^2$=22.605,
231 *P*=0.000), chemotherapy cycles ($\chi^2$=13.957, *P*=0.000), and prescription dose
232 ($\chi^2$=10.446, *P*=0.005) as the significant factors affecting the prognosis.

233

234 **Discussion**

235 At present, there are no standard treatment regimens for esophageal cancer recurrence.
236 The 2016 guidelines issued by Union for International Cancer Control (UICC)
237 recommended that the recurrence after surgery should be treated with concurrent
238 chemoradiotherapy, while combined chemotherapy based on fluorouracil or taxanes
239 can be used as the preferred concurrent chemoradiotherapy. Moreover, patients with the
240 recurrence after surgery may receive surgery, chemotherapy, and palliative support
241 treatment. Clearly, the above recommendation was made based on the non-surgical
242 treatment mode of esophageal cancer, a retrospective analysis of a small sample size,
243 and indirect evidence from other studies. Previous reports have shown that
244 chemoradiotherapy can benefit the survival of some patients with recurrence of
245 esophageal cancer after surgery. However, the following issues remain to be addressed
246 for each research center: the dose of radiotherapy, the range of irradiation target area,
247 the necessity of combined radiotherapy with chemotherapy, and the mode of combined
248 treatment [12, 14, 15]. So far, there have been numerous studies on chemoradiotherapy

249 administered to patients with recurrent esophageal cancer [16-21]. Among these studies,
250 the survival rates of patients varied greatly from one to another. In these cases, the
251 median survival time was 7-43 months. 1-, 2-, and 3-year survival rates were 33.8% -
252 85.7%, 15.0% - 51.3%, and 10.6% - 56.3%, respectively, while there were few reports
253 on 5-year and over five years survival rates. The above observations could be explained
254 as follows: (1) most of the studies were retrospective analysis with a small sample size;
255 (2) there were inherent biases in case selection; (3) patients either with local recurrence
256 only or with combined local recurrence and combined distant metastasis were
257 differentially included in different studies; (4) the dose and strategies of radiotherapy
258 or chemotherapy regimens varied from one study to another; (5) patients with
259 concurrent chemoradiotherapy were included in a subset of studies, while other studies
260 only involved patients with radiotherapy, and no subgroup analysis was performed.
261 Given the number of cases involved (501 patients), the present study may be the largest
262 retrospective study on chemoradiotherapy administered to patients with recurrent
263 esophageal cancer in a single research center. This study showed that the 1-, 3-, and 5-
264 year survival rates were 50.3%, 18.1% and 12.8%, respectively, while the median
265 survival time was 12.1 months. Among the total of 501 cases with local recurrence, 157
266 developed combined distant metastasis. For 344 patients with local recurrence only, the
267 1-, 3-, and 5-year survival rates were 53.6%, 22.6%, and 16.4%, respectively, and the
268 median survival time was 12.8 months.

269 Previous studies have identified various prognostic factors for patients with

postoperative recurrence of esophageal cancer receiving chemoradiotherapy [11, 12, 15, 22-25]. Among these factors, the time interval between surgery and the occurrence of recurrence has been confirmed by most studies to be an independent factor affecting the prognosis. Jingu et al.[24] retrospectively studied the clinical data of 80 patients with postoperative local recurrence of esophageal cancer by a multivariate analysis, and found that the short postoperative recurrence time is one of the independent factors affecting the overall survival of patients. Nemoto et al.[25] reported similar results in the retreatment of 33 patients with postoperative local recurrence of esophageal cancer, and identified the postoperative recurrence interval as one of the independent factors affecting the prognosis of patients. Consistently, the multivariate analysis in our study demonstrated that the interval between surgery and recurrence is among the independent factors affecting the prognosis. The analysis of 344 patients with postoperative local recurrence only further confirmed that the interval significantly affects the prognosis of patients. It has been shown that the occurrence of recurrence or metastasis in patients with esophageal cancer shortly after surgery may be related to the micro-metastasis of tumor cells[26]. It is known that esophageal cancer is a systemic disease, rather a localized one. As a local treatment, radical surgery has no effect on the micro-metastasis that occurs prior to the operation. Patients with early relapse may have a poorer biological behavior than those with later relapse, showing a prognostic difference between the two groups of patients. The TNM staging of esophageal cancer acts as an indicator of tumor biological behavior in the patients, and is closely correlated

291 with postoperative recurrence and prognosis of patients with esophageal cancer. Similar
292 to the report of Hsu et al.[27], the present study showed that postoperative N staging is
293 an independent factor affecting the prognosis of patients. The prognosis of patients with
294 postoperative recurrence and combined distant metastasis is usually poorer than that of
295 patients with recurrence only. Generally, the recurrence of esophageal cancer mainly
296 involves lymph nodes and anastomoses. Notably, clinical symptoms and signs related
297 to the recurrence, such as neck mass, hoarseness, cough, and poor swallowing appear
298 earlier, whereas other recurrence-caused clinical symptoms and signs involving lung,
299 liver, bone, brain, and other organs occur relatively late. The cancer patients detected at
300 an early stage can be diagnosed and treated in a timely manner, thereby affecting the
301 prognosis of patients. As a localized treatment regimen, radiotherapy displays a limited
302 efficacy for patients with distant metastases. And patients with esophageal cancer are
303 less sensitive to chemotherapy drugs, suggesting a limited effect of chemotherapy on
304 the patients [11, 28]. Thus, patients with combined recurrence and combined distant
305 metastasis usually have a poor prognosis. Most clinical studies have demonstrated that
306 combined chemoradiotherapy is superior to radiotherapy or chemotherapy alone,
307 providing an important treatment regimen for patients with postoperative recurrence of
308 esophageal cancer [6, 8, 12, 14-17].

309 Here, we showed that the combined chemotherapy did not affect the prognosis of
310 the whole group of patients. However, further stratified analysis revealed that
311 chemotherapy of more than two cycles led to a better prognosis in the patients, while

independently affecting the prognosis. It has been rarely studied whether the number of chemotherapy cycles has an impact on the prognosis of patients with relapsed esophageal cancer treated with chemoradiotherapy. And fewer studies on the subgroup analysis related to the cycle number of chemotherapies have been reported. Among the related studies, synchronous chemotherapy of two cycles was normally described in the materials and methods [22]. Clearly, most studies were aimed at postoperative adjuvant chemotherapy[29-31], while the cycle number of chemotherapies varied from one study to another. Rice et al.[29] and Heroor et al.[30] recommended a regimen involving postoperative radiotherapy and concurrent chemotherapy of 2 cycles. Meanwhile, Bedard et al.[31] showed that patients undergoing postoperative radiotherapy combined with chemotherapy of 4 cycles have a better prognosis. Thus, to determine the optimal cycle number of chemotherapies for patients with postoperative recurrence of esophageal cancer, prospective studies of large samples need to be conducted. Besides, the dose of radiotherapy for patients with postoperative recurrence of esophageal cancer has been an interesting issue for the physicians. Since the dose of radiotherapy is generally affected by a number of factors such as the general health status of patients during treatment, the location of the recurring lesion, administration of combined chemotherapy, and the size and scope of the lesion, there are differences in the dose of radiotherapy among the studies. At present, while there is no consensus on the radiation dose, most studies recommend that the radiation should be conducted at a dose of no less than 50 Gy. Zhang et al.[32] found that the median overall survival and progression-

333 free survival of patients with postoperative recurrence of esophageal cancer receiving
334 radiotherapy at a dose of ≥60 Gy were higher than those of patients undergoing
335 radiotherapy at a dose of <60 Gy. Thus, they recommended that the radiation dose for
336 patients with regional recurrence of esophageal cancer should be ≥60 Gy. Ni et al.[33]
337 analyzed 193 cases with postoperative recurrence of thoracic esophageal squamous cell
338 carcinoma undergoing re-therapy and observed that the prognosis of patients in high-
339 dose radiation group (≥60 Gy) was better than that in lower dose group. Shioyama et
340 al.[34] studied 82 patients with local recurrence of esophageal cancer after surgery and
341 showed that the prognosis of patients receiving ≥50 Gy irradiation was better than that
342 in lower dose group. Similar to the above findings, the present study demonstrated that
343 the patients with a radiotherapy at a dose of less than 60 Gy had a poor prognosis.
344

345 **Conclusion**

346 This study showed that chemoradiotherapy is safe and effective for patients with
347 postoperative recurrence of esophageal cancer. Male patients with late pN stage, higher
348 LODDS, chemotherapy of ≤2 cycles, recurrence time of ≤24 months, and combined
349 distant metastasis displayed a poor prognosis. Since the present study is a single-center
350 retrospective study, certain biases in case collection, number of cases between groups,
351 and treatment methods may affect the results of this study. Moreover, this study may be
352 subject to the potential influencing factors such as ECOG score, KPS score, regression
353 status, age, size and location of the recurrent lesion. Thus, a multi-center randomized

354 controlled study in a large cohort needs to be conducted to provide a more reliable basis
355 for the clinical treatment of patients with postoperative recurrence of esophageal cancer.
356
357 **Abbreviations**
358 LRR: Local regional recurrence; OS: Overall survival rate; LODDS: Log odds of
359 metastatic lymph nodes; ENI: Elective nodal irradiation; IFI: Involved-field irradiation;
360 UICC: Union for International Cancer Control
361
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364
365 **Authors' contributions**
366 WS, and YL drafted the manuscript. YK and HG participated in the design of the study
367 and performed the statistical analysis. SL, and KY conceived the study and participated
368 in its design and coordination. SZ revised the manuscript. All authors read and approved
369 the final manuscript.
370
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374 **Availability of data and materials**

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376

377 **Ethics approval and consent to participate**

378 Ethical consent was obtained from the Ethics Committee of Fourth Hospital of Hebei

379 Medical University (2020KY382) and all subjects participated in the study with a

380 written informed consent.

381

382 **Consent for publication**

383 Not applicable

384

385 **Conflict of interest**

386 The authors declare that they have no competing interests.

387

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501 **Figure legends**

502 **Fig. 1: Survival curves of the cancer patients with or without combined combined**

503 **distant metastasis.**

504 **Fig. 2: Single factor subgroup analysis curve of patients with postoperative local**

505 **recurrence only.** A: recurrence time, B: chemotherapy cycles, C: prescription dose.

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522 **Table 1 Univariate analysis of prognosis in patients with recurrent esophageal**

523 **cancer after radiotherapy (*n*=501)**

| Prognostic factors | | N | Survival rate (%) | | | Median survival rate | $\chi^2$ | *P* |
|---|---|---|---|---|---|---|---|---|
| | | | 1-yr | 3-yr | 5-yr | (months) | | |
| **Sex** | | | | | | | 11.427 | 0.001 |
| | Male | 366 | 45.3 | 14.8 | 9.2 | 11.1 | | |
| | Female | 135 | 63.8 | 26.9 | 22.1 | 16.2 | | |
| **Age** | | | | | | | 2.38 | 0.123 |
| | ≤59y | 265 | 52.4 | 19.4 | 16.5 | 12.6 | | |
| | ≥60y | 236 | 48.0 | 16.7 | 8.4 | 11.7 | | |
| **Basic diseases** | | | | | | | 0.172 | 0.679 |
| | No | 362 | 47.2 | 17.8 | 13.9 | 11.6 | | |
| | Yes | 139 | 58.6 | 19.2 | 10.3 | 13.0 | | |
| **Smoking** | | | | | | | 7.385 | 0.007 |
| | No | 238 | 57.6 | 23.0 | 15.8 | 14.6 | | |
| | Yes | 263 | 43.5 | 13.2 | 10.1 | 10.6 | | |
| **Drinking** | | | | | | | 8.079 | 0.004. |
| | No | 295 | 54.3 | 23.1 | 16.0 | 13.9 | | |
| | Yes | 206 | 44.2 | 10.6 | 7.9 | 11.1 | | |
| **Family** | | | | | | | 1.861 | 0.173 |
| | No | 429 | 49.6 | 20.1 | 14.4 | 11.9 | | |
| | Yes | 72 | 54.7 | 4.8 | 4.8 | 12.5 | | |
| **Differentiation** | | | | | | | 0.020 | 0.887 |
| | No/poorly differentiated | 107 | 46.4 | 20.4 | 15.3 | 11.3 | | |
| | Medium/highly differentiated | 394 | 51.3 | 17.6 | 12.3 | 12.3 | | |
| **Lesion location** | | | | | | | 4.640 | 0.098 |
| | Upper thoracic | 60 | 46.9 | 24.1 | 18.7 | 11.0 | | |
| | Middle thoracic | 275 | 52.0 | 21.7 | 14.8 | 12.7 | | |
| | Lower thoracic | 166 | 48.5 | 8.8 | 7.3 | 11.8 | | |
| **Thoracotomy** | | | | | | | 0.011 | 0.917 |
| | Left thoracotomy | 431 | 49.3 | 18.3 | 12.9 | 11.8 | | |
| | other | 70 | 56.7 | 17.0 | 12.1 | 13.9 | | |
| **Length of lesion in esophagography (cm)** | | | | | | | 7.140 | 0.008 |
| | <5.0 | 218 | 54.8 | 22.7 | 18.2 | 14.2 | | |
| | ≥5.0 | 283 | 46.7 | 14.9 | 9.4 | 11.3 | | |
| **pT stage** | | | | | | | 9.607 | 0.022 |
| | pT1 | 66 | 50.5 | 18.6 | 16.2 | 12.1 | | |
| | pT2 | 100 | 61.7 | 27.1 | 20.9 | 16.1 | | |
| | pT3 | 314 | 47.5 | 15.5 | 10.4 | 11.6 | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | pT4 | 21 | 33.3 | 9.5 | 4.8 | 6.9 | | |
| **pN stage** | | | | | | | 10.214 | 0.006 |
| | pN0 | 240 | 55.5 | 24.8 | 18.0 | 13.8 | | |
| | pN1 | 171 | 45.2 | 13.8 | 9.5 | 11.0 | | |
| | pN2+3 | 90 | 45.6 | 8.1 | 4.0 | 10.0 | | |
| **Postoperative stump** | | | | | | | 0.715 | 0.398 |
| | Negative | 461 | 50.4 | 18.4 | 12.8 | 12.1 | | |
| | Positive | 40 | 48.7 | 17.2 | 17.2 | 7.7 | | |
| **Vascular tumor thrombus** | | | | | | | 4.232 | 0.040 |
| | No | 474 | 50.9 | 19.1 | 13.4 | 12.3 | | |
| | Yes | 27 | 38.9 | 3.9 | 3.9 | 8.6 | | |
| **Number of lymph nodes cleared during operation (pieces)** | | | | | | | 2.294 | 0.318 |
| | ≤9 | 206 | 51.1 | 21.3 | 15.7 | 12.3 | | |
| | 10-15 | 179 | 51.8 | 14.7 | 9.9 | 12.3 | | |
| | ≥16 | 116 | 46 | 16.9 | 11.7 | 11.3 | | |
| **LODDS** | | | | | | | 25.233 | 0.000 |
| | ≤0.030 | 271 | 57.8 | 26.4 | 19.4 | 14.3 | | |
| | >0.030 | 230 | 41.4 | 9.4 | 5.9 | 9.8 | | |
| **Postoperative chemotherapy** | | | | | | | 1.363 | 0.243 |
| | No | 227 | 45.0 | 18.8 | 12.2 | 10.1 | | |
| | Yes | 274 | 54.5 | 17.6 | 12.9 | 12.9 | | |
| **Chemotherapy cycle** | | | | | | | 19.937 | 0.000 |
| | 0-2 | 333 | 42.2 | 14.8 | 9.5 | 9.9 | | |
| | ≥3 | 168 | 66.1 | 24.4 | 19.3 | 16.9 | | |
| **Irradiation method** | | | | | | | 0.041 | 0.839 |
| | IFI | 320 | 51.2 | 17.9 | 11.1 | 12.3 | | |
| | ENI | 181 | 48.7 | 18.5 | 16.0 | 11.8 | | |
| **Radiation dose (Gy)** | | | | | | | 8.417 | 0.015 |
| | <60 | 76 | 37.8 | 9.1 | 6.8 | 9.6 | | |
| | 60 | 265 | 53.4 | 21.4 | 16.4 | 12.7 | | |
| | >60 | 160 | 50.4 | 16.9 | 10.7 | 12.2 | | |
| **Postoperative recurrence time (months)** | | | | | | | 25.616 | 0.000 |
| | ≤24 | 391 | 45.3 | 13.4 | 10.0 | 11.1 | | |
| | >24 | 110 | 67.4 | 34.1 | 19.1 | 24.8 | | |
| **Number of recurrence areas after surgery** | | | | | | | 0.520 | 0.571 |
| | 1 | 393 | 50.3 | 19.1 | 13.5 | 12.2 | | |
| | ≥2 | 108 | 49.9 | 14.6 | 10.4 | 11.8 | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Combined distant metastasis** | | | | | | 10.786 | 0.001 |
| | No | 344 | 53.6 | 22.6 | 16.4 | 12.8 | |
| | Yes | 157 | 43.4 | 9.1 | 5.5 | 11.1 | |

LODDS: log odds of positive lymph nodes

555 **Table 3 Univariate subgroup analysis results of patients with only local regional**

556 **recurrence after surgery**

| Prognostic factors | | N | Survival rate (%) | | | Median survival rate (months) | $\chi^2$ | *P* |
|---|---|---|---|---|---|---|---|---|
| | | | 1-yr | 3-yr | 5-yr | | | |
| **Postoperative recurrence time (months)** | | | | | | | 22.605 | 0.000 |
| | ≤24 | 262 | 48.2 | 16.0 | 12.0 | 11.6 | | |
| | >24 | 82 | 70.1 | 42.5 | 26.6 | 28.9 | | |
| **Number of recurrence areas after surgery** | | | | | | | 0.784 | 0.376 |
| | 1 | 274 | 55.6 | 30.6 | 17.0 | 13.4 | | |
| | ≥2 | 70 | 44.7 | 18.6 | 13.9 | 10.9 | | |
| **Postoperative chemotherapy** | | | | | | | 0.012 | 0.912 |
| | No | 156 | 50.2 | 25.8 | 16.2 | 12.2 | | |
| | Yes | 188 | 56.3 | 20.1 | 15.7 | 13.9 | | |
| **Chemotherapy cycle** | | | | | | | 13.957 | 0.000 |
| | 0-2 | 232 | 45.8 | 17.9 | 11.6 | 10.6 | | |
| | ≥3 | 112 | 68.6 | 32.1 | 26.7 | 19.4 | | |
| **Irradiation method** | | | | | | | 0.851 | 0.356 |
| | IFI | 214 | 53.4 | 21.5 | 13.5 | 12.5 | | |
| | ENI | 130 | 53.9 | 24.3 | 20.8 | 13.9 | | |
| **Radiation dose (Gy)** | | | | | | | 10.446 | 0.005 |
| | <60 | 47 | 40.0 | 10.3 | 6.9 | 9.0 | | |
| | 60 | 186 | 57.5 | 27.7 | 22.9 | 14.0 | | |
| | >60 | 111 | 52.2 | 19.1 | 11.4 | 12.3 | | |

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# Figures

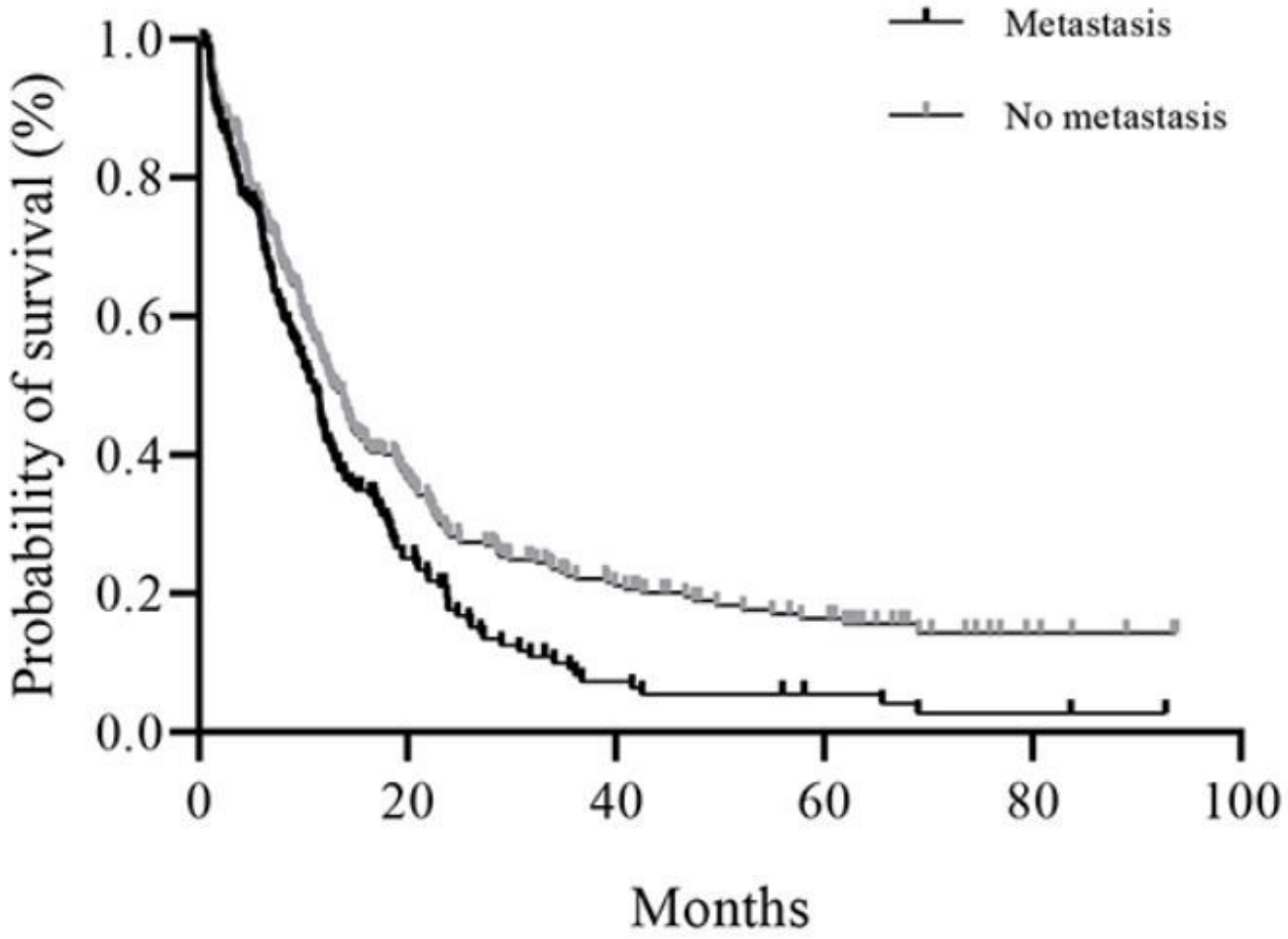


**Figure 1**

Survival curves of the cancer patients with or without combined combined distant metastasis.

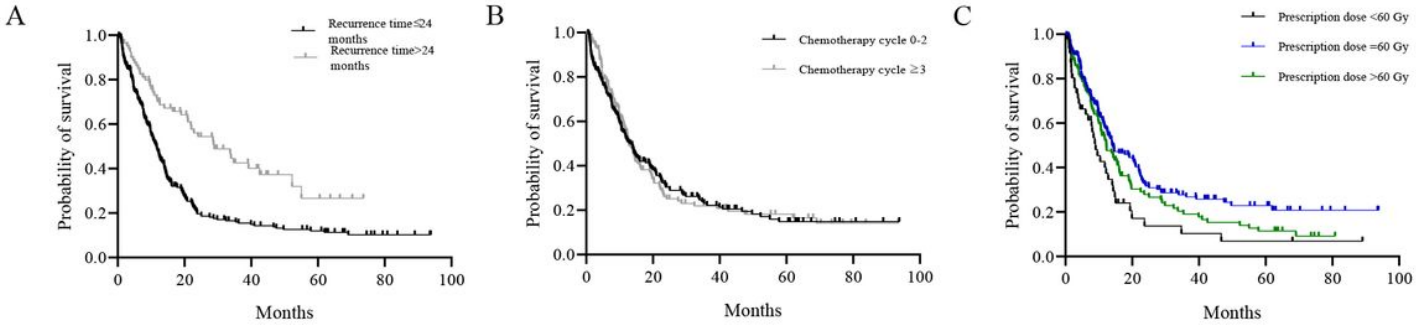


**Figure 2**

Single factor subgroup analysis curve of patients with postoperative local recurrence only. A: recurrence time, B: chemotherapy cycles, C: prescription dose.