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Surgery or radiotherapy, which is more effective for upper esophageal carcinoma? A retrospective cohort study based on 191 cases

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► ***Original article***

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ABSTRACT

Background*:** To compare radical surgery with definitive radiotherapy for upper third esophageal squamous cell carcinoma. ***Materials and Methods*:** A total of 191 patients were included in the study. Patients' clinicopathologic features, and survival time were recorded. Kaplan-Meier (K-M) analysis was adopted to analyze Overall survival (OS), Disease-free survival(DFS), Progression-free survival(PFS), and a Cox multivariate model was used to adjust potential confound factors. ***Results: The K-M survival analysis showed that treatments, location of lesion, and length of lesion were all associated with the OS (P<0.005). In the surgery group, K-M survival showed that T stage (T1 vs T2, P=0.012, T1 vs T3, P=0.002), location (upper vs upper merged middle, P<0.001), and length lesion (<5 cm vs >5 cm, P=0.015), affected the OS，T stage (T1 vs T2, P=0.018, T1 vs T3, P=0.020) and location of lesion (upper vs upper merged middle, P=0.007) was associated with DFS. The Cox model showed that none of these parameters independently influenced the OS and DFS. In the radiotherapy group, K-M survival showed that supraclavicular lymph node metastasis (P=0.007), concurrent chemo-radiotherapy (P=0.012), and sex (P=0.047) influenced the OS，adjuvant chemotherapy (P=0.013) and age (P=0.013) influenced PFS, The Cox model showed that supraclavicular lymph node metastasis (P=0.018) independently influenced OS and adjuvant chemotherapy (P=0.046) independently influenced PFS. ***Conclusion:*** Surgery has better therapeutic effect than radiotherapy. Patients with an upper merged middle lesion and advanced T stage for surgery, male, local advanced and without concurrent chemo-radiotherapy for radiotherapy have a poor prognosis.

Keywords: *Esophageal upper squamous cell carcinoma, surgery, radiotherapy.*

INTRODUCTION

According to the global cancer statistics in 2015, esophageal carcinoma was the 7th most common cancer and the 6th most common cause of cancer-related mortality in males in 2012 [(1)]. It is well known, that the prognosis of patients with esophageal cancer is poor, the average 5-year-survival rate after surgical resection is only3–20%[(2)].. Esophageal carcinoma is three to four times more common in men than in women. China accounts for almost 50% of the global rate of esophageal cancer. Squamous cell carcinoma (SCC) is still the dominant histological subtype in China, accounting for approximately 95% of cases [(3)], while adenocarcinoma (AC) accounts for around 60% of cases in Western countries [(3,4)].The importance of fact that the prognosis of squamous cell cancer is well known worse than that of adenocarcinoma [(5)].

Surgery remains the mainstay of treatment for most esophageal cancer patients with a curative intent. The goal is to achieve regional tumor control. However, many patients are unfit for surgery due to various reasons, such as advanced stage, patients' will, and the cancer location in the thoracic upper third of the esophagus. In the present study, we discuss treatment outcomes in patients with upper third esophageal cancer. Traditional views consider that this type of cancer is unsuitable for surgery; thus, radiotherapy is the main treatment in these patients. Definitive chemoradiotherapy has resulted in good long-term survival, especially in SCC patients [6-9]. However, no studies have directly compared the effect of surgery and radiotherpy/chemoradiotherapy. In NCCN guideline，there was not also recommended surgery or radiotherapy which should be preferred in upper esophagus cancer. Owing to lack evidence-based literature，in the clinical practice，most therapeutic center only according to their own experience to adopt various treatments. Therefore, we carried out this study to compare the outcome of surgery and radiotherapy/chemoradiotherapy in patients with SCC.

MATERIALS AND METHODS

Between June 2011 and June 2017, all esophageal cancer patients at Nanchong Central Hospital and other patients who received surgery or radiotherapy at other hospitals and were then admitted to our hospital for follow-up treatment were screened for inclusion in this study. The inclusion criteria were as follows: 1. Prior to surgery or radiotherapy, esophageal SCC was confirmed by pathology, and tumor location was the thoracic upper third of the esophagus [10], including the cervical merged upper and upper merged middle third of the esophagus; 2. Patients had received radical surgery or definitive radiotherapy/concurrent chemoradiotherapy, including preoperative chemotherapy, adjuvant chemotherapy (postoperative or after radiotherapy); 3. No distant metastasis; and 4. Patients had follow-up information. The exclusion criteria were as follows: 1. Adenocarcinoma, small cell carcinoma and all other types of cancer; 2. Tumor location was in the cervical, middle third or lower third of the esophagus alone; 3. Patients who had only undergone surgical exploration or had R1/R2 residual disease; 4. Patients who had received postoperative adjuvant radiotherapy six months after surgery; 5. Patients who had received targeted therapy; 6. Following surgery or radiotherapy, the survival time was shorter than 3 months; and 7. Following surgery or radiotherapy, the survival time was longer than 8 years, as during this period other censored data may have resulted in statistical bias.

As a result, 2700 patients with esophageal cancer were screened, including 252 with upper third esophageal cancer. With regard to the excluded cases, ten of the 252 patients with upper third esophageal cancer did not receive surgery or radiotherapy, eight had no follow-up contact information , 21 were lost to follow-up, 13 had postoperative adjuvant radiotherapy, four had a survival time after surgery or radiotherapy shorter than 3 months (radiotherapy three, surgery one), three had a survival time longer than 8 years (two treated with radiotherapy and the survival times were 162 and 132 months, one treated with surgery and the survival time was 96 months), and two patients only underwent surgical exploration. Finally, 191 cases were selected according to the inclusion criteria, 112 in the surgery group and 79 in the radiotherapy group. Eighty-five cases had single upper esophageal cancer, and 61 of these cases underwent surgery and 24 received radiotherapy. The flow diagram of screening patients are shown in figure 1. OS was defined the time after treatment to die which caused by any reasons, DFS was defined the time after radical surgery to disease recur, PFS was defined the time after the radiotherapy to disease progress. Until June 2018, there were 103 patients died (53 patients in surgery group, 50 patients in radiotherapy group). The total follow-up time was 84.00 months, the mean follow-up time was 32.69 months. There were 53 patients

recurred (25 patients recurred and 37 patients did not provide information whether recurred or the precise time of recurrence in surgery group, 28 patients recurred/progressed and 32 patients did not provide information whether recurred or the precise time of recurrence in radiotherapy group). Prior to surgery or radiotherapy, esophageal SCC was confirmed by pathology and all patients also underwent barium meal, chest computed tomography (CT), ultrasound of superficial lymph glands, and both abdominal and head Magnetic Resonance Imaging (MRI), and bone Emission Computed Tomography (ECT).

The following patient information was recorded: treatment, sex, age, lesion locati- on, lesion size, T stage, mediastinal and supraclavicular lymph node metastasis, concurr- ent chemoradiotherapy, adjuvant chemotherapy, time of recurrence, and survival time. T- hese data are shown in table 1 (some cases had missing information). In addition to these data, T stage in the surgery group was determined, and it was found that 20 cases were T1 stage, 34 were T2 stage, 49 were T3 stage, and 9 cases were Tx stage. In the radiother- apy group, no supraclavicular lymph node metastases were found in 66 cases and metas- tases were found in 13 cases. In the surgery group: no recurrences were noted in 25 cases, and recurrences were noted in 50 cases. In the radiotherapy group, no recurrences were found in 19 cases, and recurrences were noted in 28 caseThe surgical procedure involved three incisions in the neck, chest and abdomen for esophagectomy with 2/3-field lymphadenecto- my or video-assisted thoracic surgery. Radiotherapy involved three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, image-guided radiotherapy, single radiotherapy or combined with concurre- nt chemotherapy. Adjuvant chemotherapy was administered 3-4 weeks after surgery or radiotherapy for 2-4 cycles. Chemotherapy regimens were Paclitaxel plus Cisplatin/ Ne- daplatin or Docetaxel plus Cisplatin/ Nedaplatin, or other regimens. Follow-up in the first year was performed every 3 months, every 6 months in the second year, every year from year 3-5, and every 1-2 years after 5 years. When recurrence was observed, the time of recurrence following treatments were recorded.

Statistical analysis

The Chi-square test was performed to analyze the symmetry of patient information between the two groups. Kaplan-Meier (K-M) univariate analysis and the log-rank test were carried out to analyze the factors related to total survival, single lesions in the upper third group, surgery, radiotherapy and recurrence. Following K-M analysis, the Cox multivariate model was adopted to adjust possible confounded factors (Chi-square test or K-M univariate analysis significant / approximate significant factors), calculate the hazard ratio (HR) and identify independent prognostic factors. All probabilities were two-tailed and $P < 0.050$ was considered statistically significant. Statistical calculations were performed using SPSS version 17.0. (SPSS Inc, Chicago., IL).

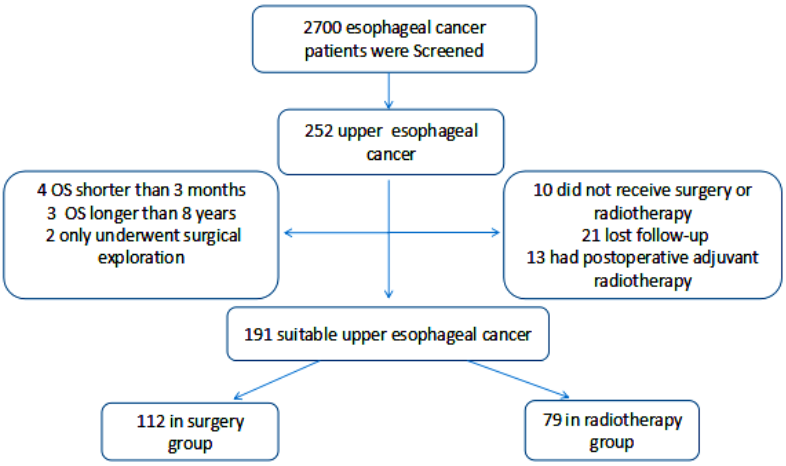

Figure 1. The flow diagram of screening patients.

Table 1. Patient characteristics in two groups.

	Surgery group (*n*=112)	Radiotherapy group (n=79)	*P**
Sex			
Male	60	40	0.689
Female	52	39	
Age (years)			
≤65	71	35	0.011
＞65	41	44	
Mediastinal _node metastasis			
No	79	47	0.023
Yes	25	31	
Unknown	8	1	
Tumor length			
＜5 cm	71	19	<0.001
≥5 cm	34	36	
Unknown	7	24	
Tumor location			
Cervical merged upper	6	12	0.006
Single upper	61	24	
Upper merged middle	32	23	
Unknown	13	20	
Single upper	61	24	0.096
Upper merged middle	32	23	
Adjuvant chemotherapy			
No	68	46	0.331
Yes	35	32	
Unknown	9	1	
Recurrence			
No	25	28	0.004
Yes	50	19	
Unknown	37	32	

*The Chi-square test did not include unknown data.

RESULTS

Total survival analysis

M survival analysis showed that treatment (surgery *vs* radiotherapy, *P*=0.002), tumor location (total, *P*<0.001, cervical merged upper *vs* upper merged middle, *P*>4.47[3], upper *vs* upper merged middle, *P*<0.001) and tumor length (<5 cm *vs* >5 cm, *P*=0.001), all influenced the OS. Although age, mediastinal node metastasis, length and location existed difference in two treatment groups (table 1), K-M survival analysis showed ages and mediastinal node metastasis did not influence the survival result (*P* >0.05), so we only included length and location into Cox model for adjusting estimated. The Cox model showed that when the location of cervical merged upper *vs* upper merged middle were included in the model in addition to treatment (*P*>4.65), length (*P*>4.[0 1]4), and location (cervical merged upper *vs* upper merged middle, *P*>4.46[0]), only location was remained influenced OS and it was an independent prognostic factor; when the location of upper *vs* upper merged middle was included in the model, in addition to treatment (*P*=0.010), length (*P*=0.984), and location (upper *vs* upper merged middle, *P*>4.445), treatment and location were both independent prognostic factors. The OS survival curves and the HRs are shown in Figures 2-4. When these factors were analyzed alone in single upper cases, K-M survival analysis showed that only treatment influenced the OS (*P*=0.003).

Survival in the surgery group

K-M survival analysis showed that T stage (total, *P*=0.001, T1 *vs* T2, *P*=0.012, T1 *vs* T3, *P*>4.446), location (total, *P*>4.445, upper *vs* upper merged middle, *P*<0.001) and length (<5 cm *vs* >5 cm, *P*=0.015), all influenced the OS. The Cox model showed that when T1 *vs* T2 was included in the model, T stage (*P*=0.094), length (*P*>4.995) and location (upper *vs* upper merged middle, *P*=0.503), were not independent prognostic factors; when T1 *vs* T3 was included in the model, T1 *vs* T3 (*P*=0.078), length (*P*=0.500), and location (upper *vs* upper merged middle, *P*>4.4[1]4), were also not independent prognostic factors. The survival curves and HRs are shown in figures 5-7.

When the factors associated with recurrence were analyzed in the surgery group, K-M analysis showed that T1 *vs* T2 (*P*=0.018), T1 *vs* T3 (*P*=0.020), and location (upper *vs* upper merged middle, *P*=0.007), were all related to DFS, but the Cox model showed that none of these parameters were independent prognostic factors.

Survival in the radiotherapy group

K-M survival analysis showed that mediastinal lymph node metastasis (P=0.007), concurrent chemoradiotherapy (P=0.013) and sex (P=0.047) all influenced the OS, and tumor location (upper *vs* upper merged middle (P>4.40 8) showed an influencing trend. When the potential confounded factor location was included in Cox adjusted model, only supraclavicular lymph node metastasis (P>4.452) was an independent prognostic factor, sex (P=0.903), tumor location (upper *vs* upper merged middle, P>4.415) and concurrent chemoradiotherapy (P=0.202) did not influence the result. The OS survival curves and HRs are shown in figures 8-10.

When the factors related to progression were analyzed in the radiotherapy group, K-M analysis showed that adjuvant chemotherapy (P>4.457), age (P>4.457), and supraclavicular lymph node metastasis (P=0.052) all influenced the PFS. When age (P=0.062), supraclavicular lymph node metastasis (P=0.246), and adjuvant chemotherapy (P=0.046) were included in the Cox model, adjuvant chemotherapy was the only independent prognostic factor.

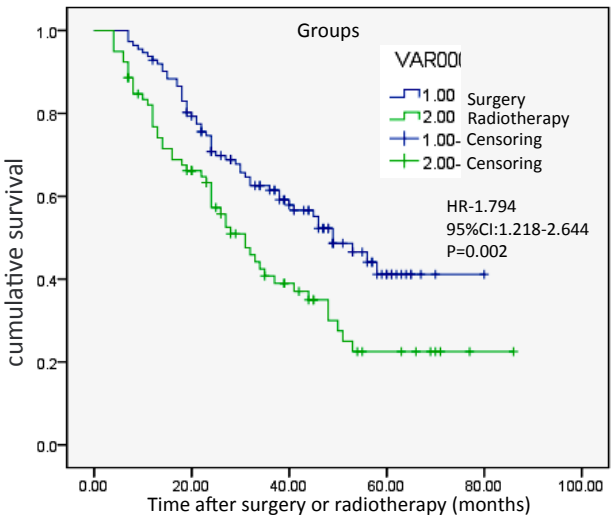

Figure 2. Total survival in the treatment groups analyzed by the Kaplan-Meier method.

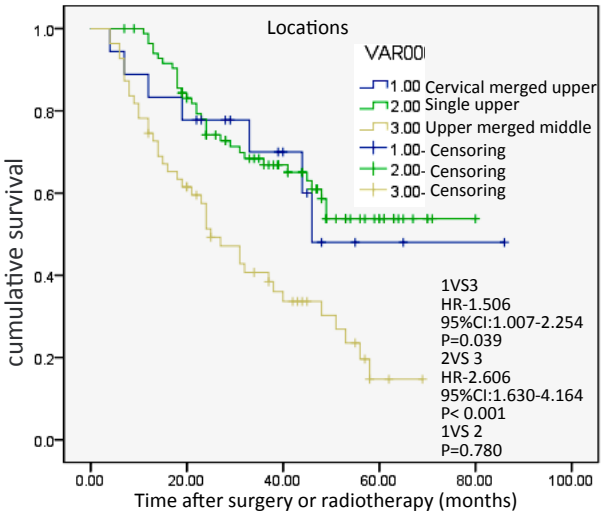

Figure 3. Total survival in relation to tumor location analyzed using the Kaplan-Meier method.

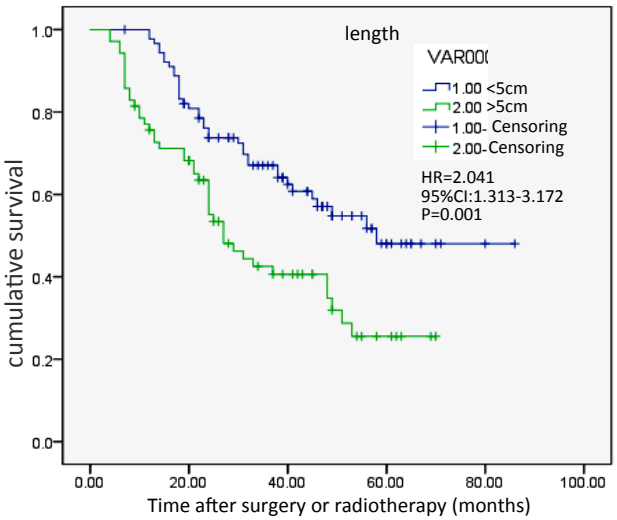

Figure 4. Total survival in relation to tumor length analyzed by the Kaplan-Meier method.

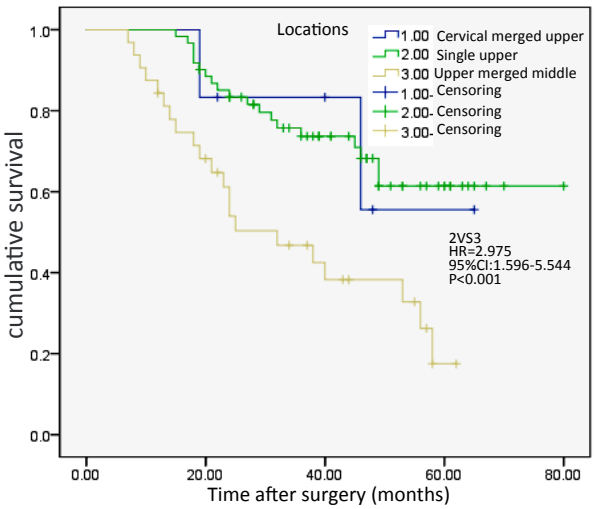

Figure 5. Survival in the surgery group related to tumor location analyzed by the Kaplan-Meier method.

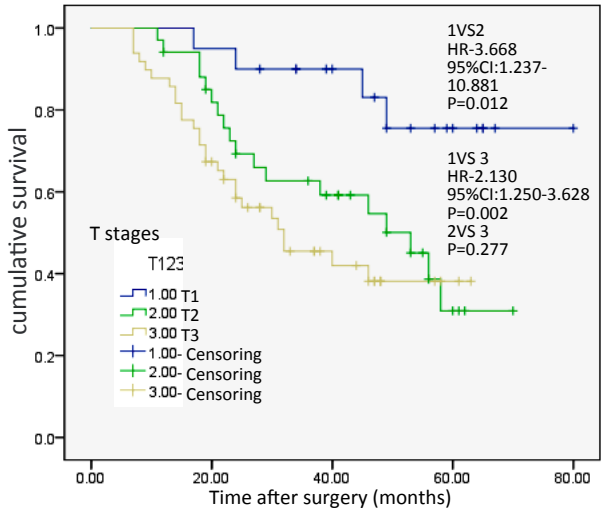

Figure 6. Survival in the surgery group related to T stage analyzed by the Kaplan-Meier method.

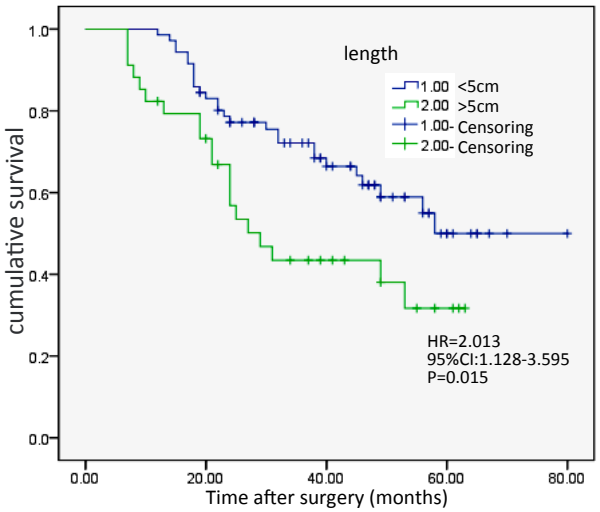

Figure 7. Survival in the surgery group related to tumor length analyzed by the Kaplan-Meier method.

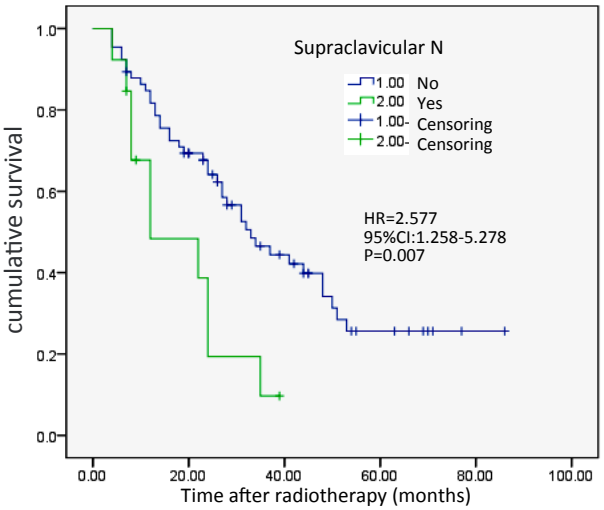

Figure 8. Survival in the radiotherapy group in relation to supraclavicular lymph node metastasis analyzed by the Kaplan -Meier method.

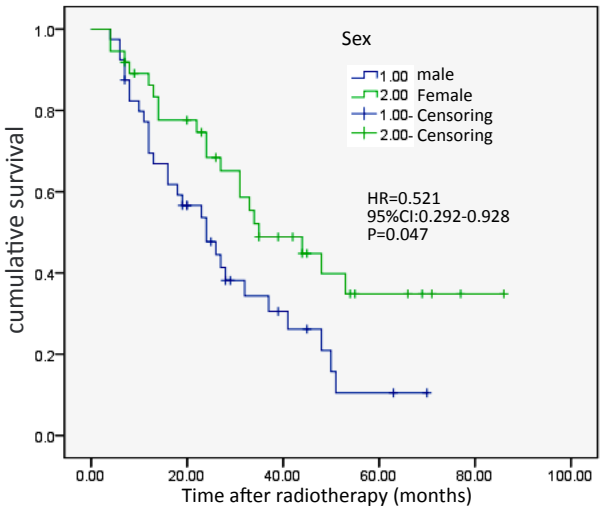

Figure 9. Survival in the radiotherapy group in relation to sex analyzed by the Kaplan-Meier method.

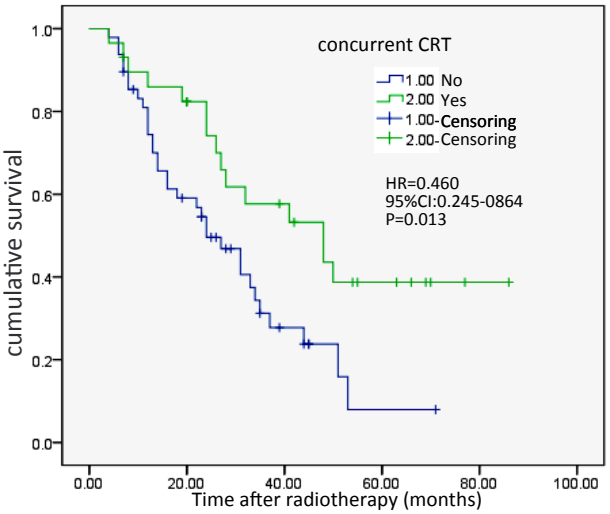

Figure 10. Survival in the radiotherapy group by concurrent chemoradiotherapy (CRT) analyzed by the Kaplan-Meier method.

DISCUSSION

Surgery in patients with upper third esophageal carcinoma is technically challenging [11-13]. During open surgery, it is difficult to achieve good exposure. Upper esophageal carcinomas characteristically not only invade non-resectable vital organs but also metastasize to the upper mediastinal and cervical nodes [14,15].Usually upper thoracic esophageal tumour requires more extensive surgery [16,17]. Residual or recurrent cancer is common [18]. Therefore, patients with upper mediastinal esophageal cancer are often excluded from surgery and treated with definitechemoradiation or radiation alone, resulting in poorer survival due to locoregional failure [19].

There are very few studies that have directly compared the outcomes of radiotherapy and surgery in upper esophageal cancer. Igaki [14] performed a retrospective study of 51 patients with T3 tumors of the upper thoracic esophagus. Gross residual primary tumor or metastasis in regional nodes invading adjacent structures was noted in 27% and incomplete resection including microscopic residual tumor was observed in 45% of patients. The overall 3- and 5-year survival rates were unsatisfactory at 20% and 12%, respectively. Papp [20] also carried out a retrospective study of 102 patients, 40 with upper third and 62 with middle third locally advanced squamous cell esophageal cancer, who received preoperative chemoradiotherapy and surgery. Following neoadjuvant chemoradiotherapy, the response rate was high (70% and 69%) in those with upper third and middle third esophageal cancer, but a significantly higher rate of pathological complete response (pCR) of 35% (14/40) was observed in upper third patients and 4.8% (3/62) in middle third patients (P<0.05). The resectability rate was similar at 70% (28/40) and 69% (43/62), respectively. This study indicated that upper third esophageal cancer was more sensitive to chemoradiotherapy.

In the present study, we directly compared the effect of surgery and radiotherapy in upper esophageal tumors. As a result surgery was significantly more effective than radiotherapy, to the best of our knowledge, this is the first report. In addition, we found the tumor location influenced survival, especially those patients who had merged locations had a poorer prognosis. This result may due to following several reasons: 1. Merged locations increased tumor length as the length influenced the survival. 2. Upper lesion compared to middle lesions may be more sensitive to radiotherapy (upper merged middle compared cervical merged upper patients increased the risk of death (RR=1.567, P =0.077)). 3.Merged locations increased the difficulty of surgery and was a disadvantageous prognosis factor (Compared with single upper lesions, patients with upper merged middle lesions had an increased risk of recurrence (HR=4.514; P=0.007)).

Our study had several advantages. First, the analysis was based on 191 cases, a large sample size. Second, we used stratified analysis in different groups/levels, such as surgery / radiotherapy /single upper groups, T stage levels, and location levels. Comparisons of means were performed in order to determine statistical significance and clinically significant factors, and avoid statistical bias. For example, in the T stage levels, although the relationships between T1, T2, T3 and surgery were statistically significant, we observed that T2 and T3 survival curves existed cross, so we analyzed the differences in T1 *vs* T1, T1 *vs* T3, and T2 *vs* T3, and found that only T1 *vs* T1, and T1 *vs* T3 were statistically significant. The same method was adopted for the analysis of lesion location. Our final stratified T stages analysis results accorded with literature reports [14, 21]. Third, we used Cox model to adjust potential confounded factor, and to determine independent prognostic factor.

There were also some disadvantages associated with this study. First, similar to the common features in all retrospective studies, bias, such as selection bias, recall bias, and confounding bias was difficult to avoid. Second, although the total sample was 191 cases, only 85 cases were included in the single upper esophagus tumor group, and the follow-up time have not over, so we remain cautious to this result that surgery is more effective than

radiotherapy in upper esophageal cancer. However, despite this shortcoming, useful information following the analysis of different tumor locations was obtained. Third, there were only 36.7% (29/79) of radiotherapeutic patients who adopted concurrent chemoradiotherapy, and most of them adopted single drug concurrent chemotherapy. As concurrent chemoradiotherapy had already proved superior to radiotherapy alone in advanced esophageal cancer [22].Therefore, we cannot infer another result that surgery is more effective than concurrent chemoradiotherapy in upper esophageal cancer. Four, there were some missing information about patients' clinicopathologic features in table 1, so we can only use a limited cases to analyze their relationship with survival.

Taken together, these findings provide relevant information on upper esophageal cancer that may help clinicians define their treatment strategies and may provide information for future research. Surgery maybe has better therapeutic effect than radiotherapy in upper esophageal cancer. Patients with an upper merged middle lesion and an advanced T stage for surgery, male, local advanced and without concurrent chemoradiotherapy for radiotherapy have a poor prognosis.

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***Conflicts of interest*: Declared none.**

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