

Comparison between different reconstruction routes in esophageal squamous cell carcinoma

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Abstract

AIM: To compare postoperative complications and prognosis of esophageal squamous cell carcinoma patients treated with different routes of reconstruction.

METHODS: After obtaining approval from the Medical Ethics Committee of the Sun Yat-Sen University Cancer Center, we retrospectively reviewed data from 306 consecutive patients with histologically diagnosed esophageal squamous cell carcinoma who were treated between 2001 and 2011. All patients underwent radical McKeown-type esophagectomy with at least two-field lymphadenectomy. Regular follow-up was performed in our outpatient department. Postoperative complica-

tions and long-term survival were analyzed by treatment modality, baseline patient characteristics, and operative procedure. Data from patients treated *via* the retrosternal and posterior mediastinal routes were compared.

RESULTS: The posterior mediastinal and retrosternal reconstruction routes were employed in 120 and 186 patients, respectively. Pulmonary complications were the most common complications experienced during the postoperative period (46.1% of all patients; 141/306). Compared to the retrosternal route, the posterior mediastinal reconstruction route was associated with a lower incidence of anastomotic stricture (15.8% *vs* 27.4%, $P = 0.018$) and less surgical bleeding (242.8 ± 114.2 mL *vs* 308.2 ± 168.4 mL, $P < 0.001$). The median survival time was 26.8 mo (range: 1.6-116.1 mo). Upon uni/multivariate analysis, a lower preoperative albumin level ($P = 0.009$) and a more advanced pathological stage (pT; $P = 0.006$; pN; $P < 0.001$) were identified as independent factors predicting poor prognosis. The reconstruction route did not influence prognosis ($P = 0.477$).

CONCLUSION: The posterior mediastinal route of reconstruction reduces incidence of postoperative complications but does not affect survival. This route is recommended for resectable esophageal squamous cell carcinoma.

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Key words: Esophageal carcinoma; Route of reconstruction; Posterior mediastinal; Retrosternal; Comparison

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INTRODUCTION

The therapeutic treatment of esophageal cancer has undergone important changes over the past several decades. For patients with localized esophageal cancer, subtotal esophagectomy with a thoracic-abdominal-cervical incision (McKeown-type esophagectomy), combined with extensive lymphadenectomy, is now generally recognized as the optimal treatment in terms of long-term survival^[1-5].

After subtotal esophagectomy, a gastric tube formed by resection of the lesser curvature is generally considered to be the most suitable esophageal substitute available^[6-10]. Reconstruction under such circumstances commonly uses either the posterior mediastinal (PM) or retrosternal (RS) route^[6,10,11]. However, the optimal route remains controversial, principally because most previous studies focused exclusively on postoperative complications and quality of life, rather than prognosis^[6-9,12].

Thus, for the first time, we conducted a retrospective study to compare not only the incidence of postoperative complications but also prognosis in patients with esophageal squamous cell carcinoma (ESCC) treated *via* the PM and RS routes.

MATERIALS AND METHODS

Patient selection

After approval was obtained from the Medical Ethics Committee of Sun Yat-Sen University Cancer Center, 306 patients diagnosed with ESCC were consecutively recruited between January 2001 and March 2011. Careful preoperative evaluations were conducted to ensure that there were no contraindications to surgical treatment. All patients included in the present evaluation underwent radical esophagectomy. Exclusion criteria included any history of malignant disease, the presence of a second primary tumor, prior non-curative resection (R1/R2), prior use of an esophageal substitute that was not a gastric tube, and any prior neoadjuvant treatment. Disease was staged based on the recommendations of the American Joint Committee on Cancer (AJCC 2010). The baseline characteristics of the 306 patients enrolled in the present study are shown in Table 1.

Surgery and complications

All patients underwent McKeown-type esophagectomy with at least two-field lymphadenectomy, as described in previous studies^[1,4,5]. Three-field lymphadenectomy was performed only if the cervical lymph nodes were thought to be abnormal upon preoperative evaluation. No definitive criteria have been established, therefore,

Table 1 Baseline patient characteristics

Characteristic	Data	Route of reconstruction (%)	
		Posterior mediastinal	Retrosternal
Age (yr)			
Median	58.3	58.6	58.2
Range	32-79	32-79	34-78
≤ 65 ¹	233	90 (75.0)	143 (76.9)
> 65	73	30 (25.0)	43 (23.1)
Sex			
Male	237	95 (79.2)	142 (76.3)
Female	69	25 (20.8)	44 (23.7)
BMI (kg/m ²)			
Median	22.3	22.2	22.3
Range	15.2-35.9	15.2-33.8	15.2-35.9
Smoking index			
Median	444.2	483.6	418.7
Range	0-3330	0-3330	0-2000
≤ 400 ²	174	67 (55.8)	107 (57.5)
> 400	132	53 (44.2)	79 (42.5)
Tumor location			
Upper thorax	46	8 (6.7)	38 (20.4)
Middle thorax	153	54 (45.0)	99 (53.2)
Lower thorax	107	58 (48.3)	49 (26.3)
pT status (UICC 7th)			
pT1	30	11 (9.2)	19 (10.2)
pT2	55	26 (21.7)	29 (15.6)
pT3	221	83 (69.2)	138 (74.2)
pN status (UICC 7th)			
pN0	139	58 (48.3)	81 (43.5)
pN1	93	36 (30.0)	57 (30.6)
pN2	53	16 (13.3)	37 (19.9)
pN3	21	10 (8.3)	11 (5.9)
Tumor grade (UICC 7th)			
G1	90	41 (34.2)	49 (26.3)
G2	168	59 (49.2)	109 (58.6)
G3	48	20 (16.7)	28 (15.1)

¹This signals the commencement of "older age" as defined by the World Health Organization (WHO); ²Risk stratification for lung cancer as defined by the WHO. BMI: Body mass index; G: Grade; pN status: Pathological node status; pT status: Pathological tumor status; UICC: International Union Against Cancer.

each reconstructive option was determined by the individual surgeon. Pyloroplasty was performed if a patient showed abnormal gastric motility preoperatively. Neither a manubrium nor a partial clavicle was reconstructed.

Complications that occurred during hospital stay and during long-term follow-up were recorded. These included anastomotic leakage, chylothorax, pulmonary complications, cardiac complications, and recurrent laryngeal nerve (RLN) palsy. Drainage, conservative management, symptomatic and function-supportive treatment, and observation, respectively, were used as initial treatments. The treatment of choice for anastomotic stricture (the options included bougienage and stent placement) depended on the extent and history of the stricture. Surgical details, and complications, are summarized in Table 2.

Follow-up

After completion of primary treatment, patients were followed up in our outpatient department every 4-6 mo for the first 3 years and every 12 mo thereafter. Radio-

Table 2 Complications arising when either route of reconstruction was used

Variable	Route of reconstruction (%)		P value
	PM	RS	
No. of patients	120	186	
Lymphadenectomy			
Three-field	29 (24.2)	32 (17.2)	
Two-field	91 (75.8)	154 (82.8)	0.137
Pyloroplasty	5 (4.2)	9 (4.8)	0.784
Anastomosis			
Left neck	110 (91.7)	176 (94.6)	
Right neck	8 (6.7)	6 (3.2)	
Intrathoracic	2 (1.7)	4 (2.2)	0.360
Thoracic duct			
Reserved	27 (22.5)	80 (43.0)	
Ligation	80 (66.7)	104 (55.9)	
Resected	13 (10.8)	2 (1.1)	< 0.001
Surgical bleeding (mL)	242.8 ± 114.2	308.2 ± 168.4	< 0.001
Complications (short-term)			
Anastomotic leakage	15 (12.5)	23 (12.4)	
Cervical	13 (10.8)	19 (10.2)	
Intrathoracic	1 (0.8)	2 (1.1)	
Mediastinal	0 (0)	2 (1.1)	
Esophagotracheal	1 (0.8)	0 (0)	0.573
Chylothorax	2 (1.7)	17 (9.1)	0.008
Pulmonary	50 (41.7)	91 (48.9)	0.214
Cardiac	16 (13.3)	20 (10.8)	0.494
RLN palsy	22 (18.3)	31 (16.7)	0.707
Complications (long-term)			
Anastomotic stricture	19 (15.8)	51 (27.4)	0.018

PM: Posterior mediastinal; RS: Retrosternal.

therapy and/or chemotherapy and/or surgical resection were adopted if and when local recurrence and/or metastasis occurred. The chosen treatment modality was determined by consideration of symptoms, the physical condition of the patient, and the clinical stage of disease. Patient-specific therapeutic schedules used the best available remedies at any time. Survival status was explored *via* direct telecommunication with patients or family members in October 2011.

Statistical analysis

We used SPSS 19.0 (SPSS, Inc., Chicago, IL) for statistical analysis. Overall survival (OS) was defined as the interval from the date of surgery to the date of death or final clinical follow-up. Correlations between the reconstructive route and clinicopathological characteristics and postoperative complications were assessed using the *t* and χ^2 tests. To detect factors associated with an increased risk of chylothorax, crude and adjusted analyses were performed using both univariate and multivariate logistic regression. Survival was analyzed *via* the Kaplan-Meier method and the differences between curves were assessed with the aid of the log-rank test. Multivariate Cox's regression analysis was performed with inclusion of parameters that prior univariate analysis had identified as significant. $P < 0.05$ was considered to be significant.

RESULTS

Of the 306 patients, 120 and 186 were treated *via* PM

Table 3 Association between recurrent laryngeal nerve palsy, lymphadenectomy, and development of an anastomotic fistula

Variable	Recurrent laryngeal nerve palsy (%)	P value
Lymphadenectomy		
Three-field	15 (24.6)	
Two-field	38 (12.4)	0.094
Anastomotic fistula		
No	42 (15.6)	
Yes	11 (28.9)	0.043

and RS reconstruction, respectively. Baseline patient characteristics are summarized in Table 1.

Pulmonary complications were the most common during the perioperative period (46.1% of all patients; 141/306). Patients in the RS group were more likely to preserve the thoracic duct ($P < 0.001$). The mean blood loss was 282.6 mL for the entire cohort and was 65.4 mL greater in the RS group than in the PM group ($P < 0.001$). A positive association between development of chylothorax and use of the RS route was observed ($P = 0.008$). Anastomotic stricture, the combined incidence of which was 12.4% (38/306), was more common in the RS than in the PM group ($P = 0.018$). Details of the operations and complications are listed in Table 2. Upon subgroup analysis, RLN palsy was found to be highly associated with three-field lymphadenectomy ($P = 0.094$) and anastomotic fistula ($P = 0.043$) (Table 3).

The median follow-up interval was 32.1 mo for surviving patients. A total of 201 patients were alive at last follow-up. The predicted 1-, 3- and 5-year overall survival rates after primary surgery were 75%, 60% and 50% respectively. The median survival time was 26.8 mo (range: 1.6-116.1 mo).

Preoperative albumin level ($P = 0.009$), pT status ($P = 0.006$), and pN status ($P < 0.001$) were independent factors prognostic for survival upon uni/multivariate analysis (Table 4). However, reconstruction route was not a significant prognostic factor ($P = 0.477$; Figure 1).

DISCUSSION

In the present study of patients with histologically diagnosed esophageal squamous cell carcinoma who underwent radical McKeown-type esophagectomy with at least two-field lymphadenectomy, we compared survival and complications in patients according to whether the RS or PM route was used. Our work had the advantages that it was performed in patients with the same disease etiology treated with a uniform therapeutic modality, and who underwent long-term follow-up focusing not only on postoperative complications but also on prognosis.

We confirmed that the reconstruction route was not associated with any significant variance in the extent of cardiac ($P = 0.494$) or pulmonary ($P = 0.214$) complications, as has been shown in previous studies^[6,7,10].

The incidence of RLN palsy was 17.3% in our entire cohort, and did not differ between the PM and RS groups ($P = 0.707$). In esophagectomy patients, the

Table 4 Univariate and multivariate Cox's regression analysis predicting overall survival

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value ¹	HR (95% CI)	P value ¹
Age (yr) ²	1.642 (1.097-2.460)	0.016	1.013 (0.991-1.035)	0.245
Sex ³	0.690 (0.431-1.107)	0.124	0.690 (0.428-1.112)	0.127
BMI (kg/m ²)	0.974 (0.917-1.035)	0.400		
Smoking index ⁴	1.499 (1.019-2.204)	0.040	1.000 (1.000-1.001)	0.596
Preoperative albumin level (g/L)	0.952 (0.917-0.988)	0.009	0.949 (0.912-0.987)	0.009
Tumor location ⁵	0.872 (0.663-1.148)	0.330		
pT ⁶	1.768 (1.209-2.585)	0.003	1.708 (1.163-2.508)	0.006
pN ⁷	1.903 (1.571-2.306)	< 0.001	1.848 (1.525-2.239)	< 0.001
Tumor grade ⁸	0.984 (0.731-1.324)	0.915		
Surgical bleeding	1.001 (0.999-1.002)	0.285		
Lymphadenectomy	0.655 (0.384-1.115)	0.119	0.779 (0.454-1.339)	0.367
Reconstruction ⁹	1.157 (0.775-1.727)	0.477		

¹Cox's proportional hazards model; ²≤ 65 years of age vs > 65 years of age; ³Male vs female; ⁴≤ 400 vs > 400; ⁵Upper thoracic vs middle thoracic vs lower thoracic; ⁶pT1 vs pT2 vs pT3; ⁷pN0 vs pN1 vs pN2 vs pN3; ⁸G1 vs G2 vs G3; ⁹Posterior mediastinal reconstruction vs retrosternal reconstruction. HR: Hazard ratio; pN: Pathological node; pT: Pathological tumor.

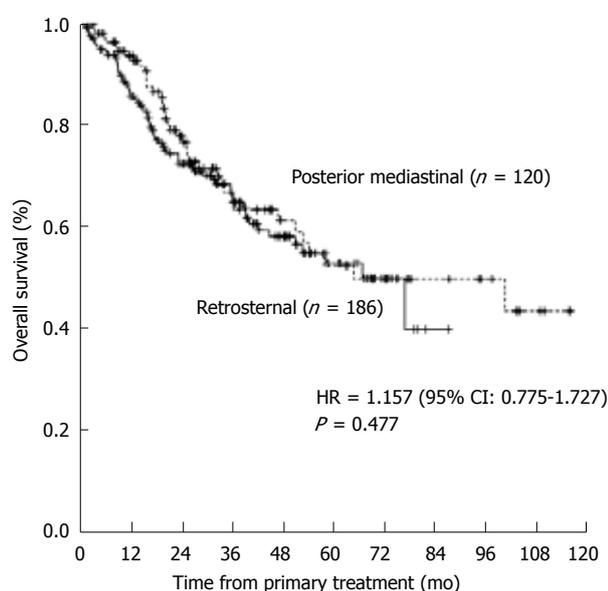


Figure 1 Kaplan-Meier curve showing overall patient survival stratified by route of reconstruction. HR: Hazard ratio.

prime etiology of RLN palsy is direct mechanical injury inflicted on the RLN during dissection^[5,13]. Fang *et al*^[14] reported that development of RLN palsy was closely linked to cervical dissection (22.9% vs 9.6%, $P = 0.089$) and anastomotic leakage (53.8% vs 13.5%, $P = 0.001$). These data lend support to our conclusion that surgical trauma and fistula-induced secondary corrosion play important roles in the development of RLN palsy (Table 3). Thus, RLN injury would be reduced if trauma during cervical lymphadenectomy were minimized and new anastomotic fistulae were managed in a timely manner.

The conduit is longer when the posterior route of reconstruction is used, therefore, a higher frequency of anastomotic leakage would be expected because a segment of stomach that is more remote from the blood supply is used (compared to the RS route)^[8,9]. However, a recent meta-analysis by Urschel *et al*^[10] showed that the

reconstruction route chosen did not affect the frequency of anastomotic fistula (95% CI: 0.35-2.94; $P = 0.98$), in agreement with our data. Additionally, we found a significant association between anastomotic stricture and use of the RS route ($P = 0.018$). After review of the literature, we suggest that patients undergoing RS reconstruction are more at risk of anatomic stricture because of the narrow entrance to the thoracic inlet and the severe foregut angulation that are created when the RS route is used^[7,11,15]. In this context, some authors recommend removal of the manubrium and the sternoclavicular joints^[16,17]. We did not take these options; rather we prioritized thoracic stability and better patient appearance. Also, application of cervical anastomosis, which permits better intraoperative exposure at the cost of more severe postoperative pressure, has been reported to decrease fistula but increases stricture development^[18]. This was not observed in our present work (anastomotic fistula, $P = 0.182$; anastomotic stricture, $P = 0.110$) (data not shown).

Chylothorax, the overall incidence of which was 6.2%, was significantly associated with use of the RS route ($P = 0.008$). However, prophylactic thoracic duct ligation or resection, which is known to mitigate against chylothorax^[19,20], was more likely to be performed in patients of the PM group ($P < 0.001$). Additionally, each reconstructive option was determined by the preference of the individual surgeon. Therefore, surgeon characteristics and decisions regarding whether to perform thoracic duct ligation or resection seemed to be the major factors contributing to the higher incidence of chylothorax observed in the RS group. The route of reconstruction may not be important, in agreement with the data of previous studies^[11,12].

Turning to surgical bleeding, Turnbull *et al*^[21] considered that such bleeding was reduced when the PM technique was used because the extent of tunneling associated with this approach is less than that required when RS reconstruction is used. This is in line with the findings of the present study ($P < 0.001$). Although bleeding

often requires blood transfusion, the clinical significance of a 64.5-mL loss of blood is marginal.

In the present study, the 5-year OS rate was 50% (median: 26.8 mo), which was better than in previous studies^[1,3]. This can be attributed to the strict enrolment criteria. Specifically, to facilitate objective comparisons, we excluded patients with pT4-stage disease, those with preoperative metastasis, and those who underwent non-radical (R1/R2) resections.

To date, the most commonly cited argument as to why the RS route of reconstruction should be favored is that it affords a radiotherapeutic advantage if local recurrence occurs^[6,7], thus contributing to a favorable prognosis. However, to the best of our knowledge, no prior study has evaluated long-term survival in patients treated *via* the RS and PM reconstructive routes. Only the biological behavior of a tumor and the chosen treatment modality could influence survival. Thus, the objective of the present study was not to verify the independently prognostic significance of a given reconstructive route but to ascertain whether the route of reconstruction influenced the efficacy of a uniform treatment modality, thereby inducing a difference in survival. To explore this question, we performed prognostic analysis but failed to demonstrate any significant survival difference according to whether the RS or PM route was used (median OS, 25.4 mo *vs* 27.4 mo; $P = 0.477$) (Figure 1). Several possible explanations may be advanced. First, improvements in patient selection and surgical techniques, especially in the context of McKeown-type esophagectomy combined with extended lymphadenectomy, have decreased the rates of local recurrence^[4,7,22]. Second, various treatment modalities (chemotherapy and/or radiotherapy and/or surgical resection) have been shown to be satisfactory in terms of efficacy and to allow acceptable levels of post-recurrence survival^[23-26]. Thus, recurrence is no longer an intractable problem for which no effective treatment is available.

Several prognostic factors were identified upon uni/multivariate survival analysis; these included preoperative albumin level and pathological stage (pT and pN status). Lower preoperative albumin levels have long been regarded as indicative of poor nutritional status, abnormal liver function, and a metabolic response to acute phase disease^[27,28]. A lower albumin level was significantly associated with a shorter survival time ($P = 0.009$). A similar result was reported by Lien *et al*^[29] in patients with adenocarcinoma of the gastric cardia. The importance of pathological stage, the best-established prognostic factor for malignant disease, was emphasized once again in our present work.

The present study has both strengths and weaknesses. The work was retrospective in nature. All work was performed in a single institution, with patients who had disease of uniform etiology and who were identically treated. However, the data may be biased to some extent, because we could not control for surgical experience or guarantee that all documentation was completely accu-

rate. However, we attempted to minimize the latter possible source of error by using consistent definitions when performing our review of records, and all data were independently checked.

In conclusion, this is believed to be the first retrospective study to investigate systematically the influence of reconstructive route on both clinical complications and prognosis. Use of the PM route of reconstruction reduces the incidence of postoperative complications, without compromising survival, and must be recommended for use in patients with resectable ESCC.

COMMENTS

Background

For patients with localized esophageal cancer, subtotal esophagectomy with a thoracic-abdominal-cervical incision (McKeown-type esophagectomy), combined with extensive lymphadenectomy, is now generally recognized as the optimal treatment in terms of long-term survival. Reconstruction under such circumstances commonly uses either the posterior mediastinal (PM) or retrosternal (RS) route. Despite studied and debated for decades, there remains no consensus as to the optimal route of reconstruction after subtotal esophagectomy.

Research frontiers

Postoperative complications and quality of life are hot topics and have been analyzed in previous studies. A recent meta-analysis showed that PM and anterior mediastinal routes of reconstruction are associated with similar outcomes.

Innovations and breakthroughs

To date, the most commonly cited argument as to why the RS route of reconstruction should be favored is that it affords a radiotherapeutic advantage if local recurrence occurs, thus contributing to a favorable prognosis. However, no prior study has evaluated long-term survival and, their results may be biased based on their small sample size. The authors' work had the advantages that it was performed in a large cohort with the same disease etiology treated with a uniform therapeutic modality, and who underwent long-term follow-up focusing not only on postoperative complications but also on prognosis.

Applications

Use of the PM route of reconstruction reduces the incidence of postoperative complications but does not affect survival. This route is recommended for treatment of patients with resectable esophageal squamous cell carcinoma.

Peer review

This paper is well written. The authors retrospectively reviewed 306 consecutive patients. They described that choice of reconstruction method was determined by surgeon preference, because there are still no criteria. Therefore, the surgeon factor should be included in all analyses. Especially in the analysis of risk for postesophagectomy chylothorax, the major factor seemed to be the surgeon and not route of reconstruction.

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