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Original Article

Comparison of larynx-preserving esophagectomy and definitive chemoradiotherapy for patients with cervical esophageal squamous cell carcinoma

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Abstract: Aim: The purpose of this study was to analyze and compare the outcomes of patients with cervical esophageal squamous cell carcinoma (ESCC) treated with larynx-preserving esophagectomy and definitive chemoradiotherapy (dCRT). Methods: One hundred and three patients with resectable cervical ESCC who underwent larynx-preserving esophagectomy or dCRT were retrospectively analyzed. Results: Fifty patients received larynx-preserving esophagectomy, and other 53 received dCRT. The median survival durations of patients in the operation and dCRT groups were 41 and 39 months, respectively (P=0.888). Among patients with stage I/II disease, patients treated surgically had significantly better disease-free survival than those treated with dCRT (P=0.048). Patients with stage III disease in the operation group had a worse overall survival (P=0.047). Eight patients who received limited cervical esophagectomy had acceptable survival rates and quality of life. Multivariate analysis revealed that stage III disease and postoperative adjuvant therapy were the independent predictive and prognostic factors of tumor recurrence and survival rates after surgeries. Clinical complete response (CR) was the independent prognostic factor of survival after dCRT. Conclusion: Larynx-preserving esophagectomy and dCRT are effective for cervical ESCC. Patients with stage I/II disease are good candidates for surgical resection; those with stage III disease are more appropriate for dCRT. For the patients who are selected carefully, limited cervical esophagectomy with direct end-to-end anastomosis of esophagus is feasible. Stage III disease and postoperative adjuvant therapy affected tumor recurrence and survival of patients after surgeries. CR was the only factor that affected the survival rates after dCRT. The optimal treatment strategy should be considered individually.

Keywords: Cervical esophageal squamous cell carcinoma, esophagectomy, chemoradiotherapy, recurrence, survival

Introduction

Esophageal cancer located in the cervical region is uncommon [1]. The cancer is very aggressive and has a poor prognosis. Traditionally, pharyngo-laryngo-esophagectomy has been the gold standard of treatment for cervical esophageal cancer. However, this radical operation has not improved the prognosis remarkably, and the associated loss of voice and permanent tracheostomy substantially compromise the quality of life [2].

In order to improve surgical safety and postoperative quality of life with esophagectomy, less radical procedures, such as larynx-preserving esophagectomy, including limited cervical esophageal resection, has been introduced [2, 3]. Definitive chemoradiotherapy (dCRT) is also an accepted treatment for cervical esophageal cancer, which preserves function well too [4-6]. Although both larynx-preserving operation and dCRT have curative and palliative effects onpatients with cervical esophageal cancer [7, 8], the relative merits of the two treatments have not been adequately evaluated, and which treatment should be preferred is unknown.

This study retrospectively compared the results of the larynx-preserving operation and dCRT for patients with cervical esophageal squamous cell carcinoma (ESCC) in order to deter-

mine which of the treatments has better outcomes. We also identified the predictive and prognostic factors that influence the recurrence of tumor and the survival rates of patients in these two modalities.

Materials and methods

Patients

Between January 2005 and December 2012, a total of 103 patients with resectable cervical ESCC were enrolled in the study. All of them were from Shanghai Chest hospital and Shanghai Renji hospital.

50 patients received operation, and the other 53 patients received dCRT. None of the patients received preoperative adjuvant therapy. Tumors were staged according to the 6th edition of the UICC staging systems.

Resectability of the tumor was confirmed by the use of computed tomography (CT), bronchofiberscopy, and/or positron emission tomography. Tumors with invasion of the trachea and vascular (carotid) sheath, or metastasis to distant organs were defined as unresectable and excluded from the study.

Curative surgery was defined as total tumor clearance achieved grossly and microscopically (R0); otherwise, it was defined as R1/R2 resection. The responses to dCRT were evaluated with endoscopy and CT. Responses were classified as complete response (CR), partial response, and stable disease.

The median follow-up period of the 103 patients was 27 (1-122) months. Complete follow-up information till death or December 2014 was available to all patients.

The Institutional Review Boards of Shanghai Chest hospital approved the study; informed consent was waived because the study was retrospective.

Treatment protocols

Operation group: Cervical or subtotal esophagectomy was performed on 50 patients with a larynx-preserving operation. Surgical resection was performed on patients in whom the distance from the inferior border of the cricoid cartilage to the oral edge of the primary tumor is ≥ 2.0 cm. Three methods of esophageal resection were used: limited cervical esophagectomy (LCE) with direct end-to-end anastomosis of the esophagus, transhiatal esophagectomy (THE), and transthoracic esophagectomy (TTE).

LCE resection with direct end-to-end anastomosis of esophagus was performed when 1) the inferior border of the tumor was above the thoracic inlet; 2) the tumor length was ≤ 3 cm; 3) T status was <3; 4) the total length of transected segment was within 5 cm; 5) there were no signs of lymph node involvement. The neck of these patients was maintained in the flexed position for 7-10 days after the operation. Because of the relatively short distance of the resection margin and the risk of local recurrence, the esophagectomy was followed by adjuvant radiotherapy or sequential chemoradiotherapy to the tumor bed and its drainage areas. Other patients with no mediastinal lymph node involvement were operated with THE, and those with it were operated with the transthoracic approach. LCE and THE were less invasive, but radical dissection was impossible. TTE allowed a mediastinal node dissection to be performed. Open laparotomy was used, and the stomach was delivered to the neck and anastomosed to restore alimentary tract continuity.

Elective unilateral or bilateral dissection of cervical lymph nodes was performed on all patients, with removal of visible and palpable nodes. Most patient received adjuvant therapy with chemotherapy, radiotherapy, or both given sequentially, unless there were contraindications or the patient declined.

Definitive chemoradiotherapy group: 53 patients, with tumor in comparable stages to those in the operation group, received concurrent dCRT as the main treatment. The field of radiation covered the gross tumor, with an additional radial margin of at least 1.0 cm and longitudinal margins of at least 3.0 cm. Adjacent involved lymph nodes were included in the radiation field as well. Intensity-modulated radiotherapy was given in a three-dimensional conformal approach to a total dose of 50-60 Gy, with a daily fraction of 2.0 Gy, five days a week. Chemotherapy was started concurrently on the first day of radiation therapy, with platinum-based doublet chemotherapeutic regimens. Two to three cycles of consolidated chemother-

Table 1. Comparison of characteristics between the operation and dCRT groups

Factors	operation group (n=50)	dCRT group (n=53)	p
Age (years, mean ± SD)	60.8±8.37	58.7±7.04	0.170
Gender			0.401
Male	29 (58%)	35 (66%)	
Female	21 (42%)	18 (34%)	
Tumor characteristics			
T status			0.652
1-2	14 (28%)	17 (32.1%)	
3-4	36 (72%)	36 (67.9%)	
N status			0.013
negative	33 (66%)	22 (41.5%)	
positive	17 (34%)	31 (58.5%)	
Stage			0.454
I/II	31 (62%)	29 (54.7%)	
III	19 (38%)	24 (45.3%)	
Tumor length			0.018
≤ 4 cm	40 (80%)	31 (60.4%)	
>4 cm	10 (20%)	22 (39.6%)	
Curability			
R0 (CR)	43 (86%)	37 (69.8%)	0.049
R1/R2 (PR+SD)	7 (14%)	16 (30.19%)	
Recurrence	22 (44%)	27 (50.9%)	0.608
Morbidity	12 (24%)	20 (37.7%)	0.132
Number of deaths	25 (50%)	26 (49.1%)	0.296
2/3/5-year OS			
Overall	61.7%/57.3%/44.1%	65%/53.5%/31.6%	0.888
Stage I/II	80.4%/76.7%/65.6%	65.5%/54.7%/41.0%	0.189
Stage III	31.6%/26.3%/8.8%	64.0%/51.7%/15.5%	0.047
2/3/5-year DFS			
Overall	65.1%/54.8%/54.8%	59.3%/51.3%/44.9%	0.435
Stage I/II	83.3%/73.2%/73.2%	59.6%/51.1%/42.6%	0.048
Stage III	37.5%/28.1%/28.1%	58.8%/50.4%/50.4%	0.390

dCRT definitive chemoradiotherapy; CR complete response; PR partial response; SD stable disease; OS overall survival; DFS disease-free survival.

apy followed the concurrent chemoradiotherapy, with the same chemotherapeutic regimen given at a 3-week interval, based on the tolerance and compliance of the patients.

Statistical analysis

Data were statistically analyzed by the use of the Student's t-test and chi-square test as appropriate. The Kaplan-Meier method was used to determine the survival of patients in each group, and comparison was made with a log-rank test. The logistic regression model was used to analyze the predictive factors of recurrence. The Cox proportional hazards regression model was used to analyze the prognostic factors of survival. A value of P <0.05 denoted statistical significance. All the calculations were performed with SPSS software for Windows (version 19.0; SPSS Inc, Chicago, III).

Results

The demographic data of the patients in the two groups were presented in **Table 1**. There were no significant differences in age, sex, T status, or tumor staging between the two groups. However, the dCRT group contained more patients with lymph node positivity (58.49% vs 34%) and tumor length >4 cm (39.62% vs 20%).

Treatment

Of the 50 patients who underwent surgical resection, 21 each underwent primary TTE and THE, respectively; eight patients underwent LCE. 43 patients (86%) had an R0 resection, and seven had an R1/R2 resection. 35 (70%) patients received adjuvant therapy: chemotherapy, six; radiotherapy, 13; and sequential chemoradiotherapy, 16.

dCRT was given to 53 patients. Thirty-seven (69.8%) of the patients had CR after treatment; 14 reached partial response; two reached stable disease. No patients had evident tumor progression.

Morbidity and mortality

The morbidity and mortality after treatment were similar in the two groups.

Table 2. Comparison of recurrence subgroup analyses between the operation and dCRT groups

Factors	Operation group	dCRT group	p
Loco-regional distribution			0.093
Tumor	6/14 (42.9%)	13/18 (72.2%)	
LN	8/14 (57.1%)	5/18 (27.8%)	
Stage			
Stage I/II	7/31 (22.58%)	13/28 (46.43%)	0.053
Stage III	15/19 (78.95%)	14/25 (56%)	0.112

dCRT definitive chemoradiotherapy.

In the operation group, the percentage of theoverall complications was 24%. Anastomotic leakage was identified in six patients. With increased postoperative nutrition and conservative treatment, the leaks were resolved, but three of the patients developed anastomotic stenosis (which was treated effectively by repeated endoscopic dilation). Three patients developed postoperative unilateral recurrent laryngeal nerve palsy, and three had postoperative pneumonia. The hospital mortality rate was 2% (n=1). Especially noteworthy, no severe complications occurred in the eight patients who were treated with LCE.

Among patients treated with dCRT, the figure of the overall complications was 37.7%. Three patients suffered serious bone-marrow suppression, one of whom was excluded from the study because of not being able to complete the regimen. Six patients developed esophageal fistula. Eight patients suffered acute serious radioactive esophagitis, and four of them developed esophageal stricture, which required repeated endoscopic dilation. Four patients developed serious radiation pneumonia. One patient died of laryngospasm six months after treatment. The hospital mortality in the dCRT group was 1.89% (n=1).

Recurrence analysis

Postoperative follow-up studies identified recurrence in 22 (44%) of the 50 patients treated with operation, including 17 (39.5%) of 43 patients with R0 resection. In the 53 dCRT-treated patients, tumor recurrence was detected in 27 (50.94%), including 18 (48.6%) of 37 patients with CR. The median recurrence time was 13 months in the operation group and 10.5 months in the dCRT group. Recurrence in the two groups was more often loco-regional than distant metastasis. Subgroup analysis revealed that recurrence was more frequent in patients with stage I/II disease in the dCRT group than that in the operation group, although the difference did not reach statistical significant (46.43% vs 22.58%, P=0.053). The incidence of recurrence of the two groups with stage III disease was similar. The data also revealed that loco-regional recurrence rate was similar in the two groups, but local tumor recurrence was more often in the dCRT group and that lymph-node recurrence was more common in the operation group (**Table 2**).

A multivariate analysis was performed to evaluate which factors, if any, were independent predictive factors in the two groups. In the operation group, univariate analysis of data from the 49 patients showed that tumor length >4 cm, T3-4 status, LN positivity, disease stage III, R1/R2 resection, and postoperative adjuvant therapy were the factors that affected tumor recurrence after surgery. These factors were then put into a multivariate analysis. The results revealed that disease stage III (OR 4.408, 95% CI: 1.983-9.798; P=0.000) and postoperative adjuvant therapy (OR 0.157, 95% CI: 0.030-0.827; P=0.029) were the independent predictive factors of tumor recurrence after operation. Thus, patients with stage III disease had higher possibilities of tumor recurrence, while patients who had received postoperative adjuvant therapy reduced tumor recurrence (**Table 3**). Unfortunately, no independent predictive factors of tumor recurrence were identified by univariate and multivariate analysis in dCRT group (data not shown).

Survival analysis

The overall median survival was 41 months for patients treated with operation and 39 months for patients treated with dCRT. The overall 2-, 3-, and 5-year survival rates for the operation group were 61.7%, 57.3%, and 44.15%, respectively, while the corresponding rates in the dCRT group were 67.6%, 51.3%, and 33.9%. The difference of the mean survival time between the two groups was not statistically significant (P=0.888) (**Table 1**). Further analysis, stratified by tumor stage, was performed to

Table 3. Univariate and multivariate analysis of factors related to recurrence of the operation group (n=49) (logistic regression)

Factors	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Gender (Female)	0.659	0.210-2.068	0.475			
Age (≥ 70)	1.078	0.281-4.139	0.912			
Tumor length (>4 cm)	7.429	1.384-39.866	0.019			
T status (3-4)	2.739	1.209-6.202	0.016			
LN positive	6.644	1.834-24.077	0.004			
Stage (III)	3.586	1.792-7.176	0.000	4.408	1.983-9.798	0.000
Curability (R1/R2)	10.125	1.116-91.879	0.040			
Adjuvant therapy	0.314	0.087-1.138	0.078	0.157	0.030-0.827	0.029

OR odds ratio; CI confidence interval.

compare the survival rate between the two groups. The patients with stage I/II disease in the operation group had a better disease-free survival (DFS) (P=0.048) than did those in the dCRT group. The 2- and 5-year DFS were 83.3% and 73.2% in the operation group and 59.6% and 42.6% in the dCRT group (**Table 1**; **Figure 1A**). However, the patients with stage III disease in the operation group had a worse overall survival (OS) than those in the dCRT group (P=0.047). The 2- and 5-year OS were 31.6% and 8.8% in the operation group and 64% and 15.5% in the dCRT group (**Table 1**; **Figure 1B**). In the operation group, the eight patients treated with LCE had a good OS, and the 5-year OS reached 87.5%.

Prognostic factors for survival in the two groups were analyzed. Among patients in the operation group, only disease stage III (HR 3.053, 95% CI: 1. 832-5.088; P=0.000) and postoperative adjuvant therapy (HR 0.239, 95% CI: 0.092-0.621; P=0.000) were independent prognostic factors. Patients with stage III disease had worse survival rates, but patients who received postoperative adjuvant therapy had improved survival rates. T3-4 status (P=0.021), tumor length >4 cm (P=0.01), lymph-node positivity (P=0.004), and R1/R2 resection (P=0.015) appeared to be prognostic factors after univariate analysis but not after multivariate analysis (**Table 4**). In the dCRT group, multivariate analysis revealed that only CR was an independent prognostic factor of survival (HR=0.371, 95% CI: 0.163-0.847; P=0.019). That is, patients with CR after dCRT had better survival rates.

Discussion

In this study, we sought to determine the optimal treatments of cervical ESCC by comparing the outcomes of patients treated with larynx-preserving esophagectomy and with dCRT. The most important finding was the differences in subgroup comparisons, although both of the two treatment modalities were effective for cervical ESCC, and the median survival duration and overall complication rates of patients in the two treatment groups were similar.

Differences in outcome in subgroup analysis of patients treated surgically and with dCRT are these: Patients with stage I/II disease in the operation group had significantly better DFS than those in the dCRT group. In contrast, patients with stage III disease in the operation group had worse OS. Moreover, our study showed that recurrence in patients with stage III disease in the operation group was significantly more frequent than that in those with stage I/II disease (78.95% vs 22.58%, P=0.000). Multivariate analysis also revealed that Stage III disease was the independent predictive or prognostic factors for tumor recurrence and survival after surgery. In view of these data, we suggest that patients with stage I/II cervical esophageal cancer are good candidates for surgical resection, whereas those with stage III disease should be regarded as having systemic disease and cannot be operated upon as if they only had local tumor. Thus, dCRT is the most appropriate option for patients with stage III disease, even if it was judged to be surgically resectable.

In our study, tumor recurrence after operation and dCRT was more often loco-regional than distant metastasis. Similar results have been reported [9]. Subgroup analysis showed that local tumor recurrence occurred more frequently in the dCRT group, which may indicate that some tumors did not actually respond completely to dCRT. For these patients, salvage

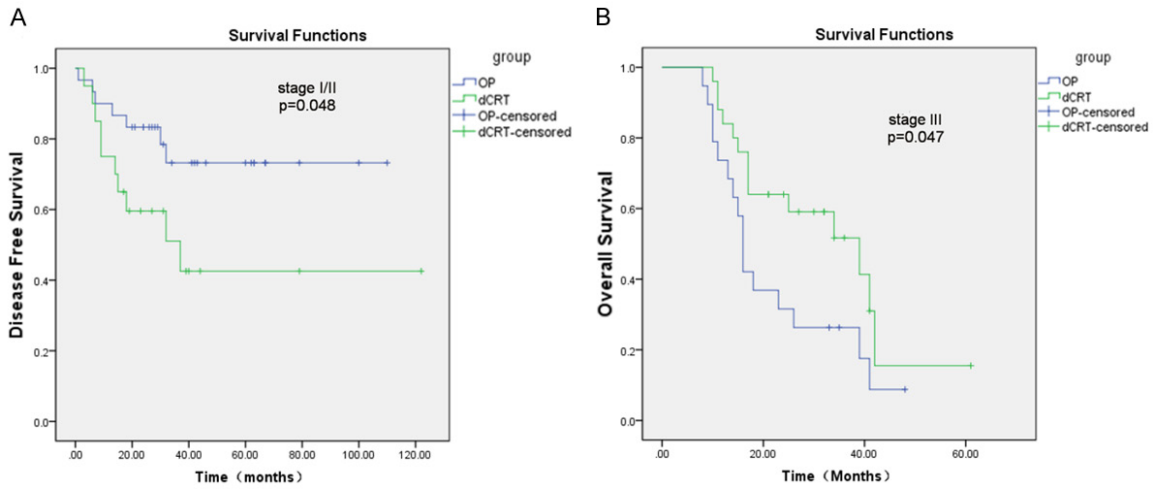

Figure 1. A. Disease-free survival of patients with stage I/II cervical esophageal squamous cell carcinoma in operation group (OP) and definitive chemoradiotherapy (dCRT) group; B. Overall survival of patients with stage III cervical esophageal squamous cell carcinoma in operation group (OP) and definitive chemoradiotherapy (dCRT) group.

Table 4. Univariate and multivariate analysis of factors related to overall survival of the operation group (Cox regression) (n=49)

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (≥ 70)	1.645	0.603-4.486	0.331			
Tumor length (>4 cm)	3.217	1.320-7.843	0.010			
T status (3-4)	2.356	1.137-4.883	0.021			
LN positive	3.466	1.473-8.151	0.004			
Stage (III)	2.527	1.590-4.015	0.000	3.053	1.832-5.088	0.000
Curability (R1/R2)	3.285	1.263-8.543	0.015			
Adjuvant therapy	0.415	0.176-975	0.044	0.239	0.092-0.621	0.003

HR hazard ratio; CI confidence interval.

resection may be the only therapeutic option that can save them from local failure, even though long-term survival after salvage resection is limited [10]. Our data also showed that loco-regional lymph node recurrence was more common after surgical resection. Perhaps more extensive lymphadenectomy could reduce this recurrence rate.

Several studies have suggested that esophageal carcinoma may benefit from combined treatment [11-13]. Ando et al. [11] have reported that, in patients with esophageal carcinoma, postoperative chemotherapy with cisplatin and fluorouracil helps prevent recurrence after operation. Wang et al. [13] have reported that adjuvant radiotherapy contributed to an improved outcome from surgery of squamous cell carcinoma in the pharyngoesophageal junction. Multivariate analysis in this study also revealed that adjuvant therapy following surgery was associated with reduced tumor recurrence and improved survival. Based on the findings of this and the previous studies, we propose that adjuvant therapy is beneficial in the surgical treatment of cervical esophageal cancer.

In this study, multivariate analysis identified CR as the only independent prognostic factor of survival in the dCRT group. Thus, cervical ESCC patients treated with dCRT should try to achieve CR. Perhaps finding biomarkers to predict CR for dCRT is worthwhile.

In this study, 50 patients received larynx-preserving esophagectomy for cervical ESCC. The 5-year overall survival rate, the complication rate and the mortality rates were 44.2%, 24% and 2%, respectively, which were similar to the reported rates [14-16]. Miyata et al. [15] also demonstrated that, compared with pharyngo-laryngo-esophagectomy, larynx-preserving esophagectomy did not negatively influence patients' prognosis. A major concern regarding larynx preservation is the tumor residue in the proximal margin. Miyata et al. [15] proposed that the larynx-preserving operation was a satisfactory procedure when the distance between

the oral edge of the primary tumor and the inferior border of the cricoid cartilage was >1.0 cm. From our experience, the proximal margin of the esophagus should be no less than 2 cm from the tumor edge, which is similar to the practice of Shiozaki et al. [17]. In our study, seven patients received R1/R2 resections, but they were all for tumor infiltration to the trachea and no tumor was found at the proximal edge. The possibility of postoperative aspiration pneumonia, which was caused by recurrent laryngeal nerve palsy partly, is another major concern about the larynx-preserving operation. No cases of recognized aspiration occurred in our series, perhaps in part because of careful dissection and preservation of recurrent laryngealnerve and quality postoperative care. Therefore, the larynx-preserving operation appears to be a favorable treatment for selected cervical esophageal cancer, with the advantage of preserving laryngeal function, and without worsening the prognosis.

Eight patients with early and localized diseases received primary limited cervical esophageal resection with direct end-to-end anastomosis of the esophagus in this study. No residual tumor was found in the proximal and distal resection margins, and no leakage or other serious complications occurred. All eight patients had an acceptable survival rate and quality of life. Nikbakhsh et al. [18] and Tavecchio et al. [19] also concluded that, in selected cases, segmental resection of primary cervical esophageal cancers, reconstructed by end-to-end pharyngoesophagostomy, is technically feasible, with acceptable postoperative cervical leakage rates, local stricture formation, and quality of life. Although the risk of leak due to surgical stress may be higher than that from the usual reconstruction technique, careful dissection of the thoracic esophagus and maintaining the neck in the flexed position during a postoperative period of about 7-10 days, seem to enable reliable reconstruction. In view of these results, we should consider selecting the patients with cervical esophageal cancer carefully. As an optional operative procedure of limited cervical esophageal segmental resection, cervical esophagectomy with a free jejunal graft interposition has gained popularity [9, 20]. However, this technique is limited by the need for a microvascular anastomosis, which is associated with significant rates of anastomotic leak and stricture suffered from autografted jejunum necrosis [21].

There are inevitably some limitations in our study. The major drawback is that it is a retrospective study. Although the basic variables and characteristics of the two groups are not significantly different, the two populations are not absolutely clinically identical. Secondly, this was a small study. Thus, it was underpowered to see the difference between the two groups, and was unable to determine in detail the effectiveness and appropriateness of each adjuvant therapies. Larger series of prospective randomized studies should be conducted in the future to support our conclusions if possible.

In conclusion, both larynx-preserving esophagectomy and dCRT are effective for treatment of cervical esophageal cancer. Patients with stage I/II disease are good candidates for surgical resection, whereas those with stage III disease are more appropriate for dCRT. For patients selected carefully, primary LCE with direct end-to-end anastomosis of esophagus is feasible. Postoperative adjuvant therapy can reduce tumor relapse and improve survival significantly. CR is the only independent prognostic factor for survival after dCRT. The optimal treatment strategy for cervical ESCC should be considered individually.

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Disclosure of conflict of interest

None.

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