·Clinical Research·

Prognostic analysis of the patients with stage-III esophageal squamous cell carcinoma after radical esophagectomy

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[Abstract] Background and Objective: Most patients with esophageal carcinoma have disease in the locally late stage (stage III) when first diagnosed, with surgery as the first treatment of choice. This study analyzed the clinical data of patients with esophageal squamous carcinoma after radical esophagectomy and investigated prognostic factors. **Methods:** The data of 361 patients with esophageal squamous carcinoma who underwent radical esophagectomy and were hospitalized at Sun Yat-sen University Cancer Center between January 1997 and March 2004 were analyzed. The Kaplan-Meier method was used to analyze prognosis, log-rank test was used to compare the groups, and the Cox proportional hazards model was used for multivariate analysis. **Results:** The 1-, 2-, 3-, 4-, and 5-year survival rates were 67.7%, 40.6%, 27.5%, 23.4%, and 20.1%, respectively. Based on univariate analysis, the degree of invasion, rate of lymph node metastasis, number of metastatic regions, number of metastatic lymph nodes, postoperative complications, and duration of surgery were prognostic factors. Based on multivariate analysis, the degree of invasion, rate of lymph node metastasis, and postoperative complications were independent factors for the prognosis. **Conclusions:** Of all clinical and pathologic factors, the degree of invasion, rate of lymph node metastasis, and postoperative complications were independent prognostic factors for the patients with stage-III esophageal squamous carcinoma after radical esophagectomy.

Key words: Esophageal carcinoma, surgery, prognosis

Esophageal carcinoma is a common malignancy in China, and surgery is the main modality for its treatment. In clinical settings, most patients with esophageal carcinoma have the disease in advanced stages at the initial evaluation (predominantly stage III)[1]. Thus, the present study reviewed patients with stage-III esophageal squamous carcinoma who underwent radical esophagectomy, in an attempt to investigate the factors associated with clinical outcomes.

Data and Methods

Patient inclusion

Patients in our study met all of the following inclusion criteria. (1) Patients had stage-III carcinoma classified according to the 2002 staging system of the International Union Against Cancer (UICC) (6th edition). (2) Distant metastasis were excluded preoperatively. (3) Patients had not undergone chemotherapy or radiotherapy before surgery. (4) Patients underwent radical esophagectomy, including at least conventional extended two-field lymphadenectomy. (5) Squamous carcinoma was confirmed on pathology. (6) Patients were followed to either death or for at least 5 years. (7) The site of the carcinoma was in the thoracic esophagus.

Patients who satisfied one of the following criteria were excluded: (1) those with other coexisting carcinomas; (2) those that received radiotherapy or chemotherapy before surgery; (3) those that underwent palliative surgery (carcinoma cells were identified microscopically on the residual end, residual carcinoma or lymph nodes, or the use of a silver clamp as marker); (4) those with inadequate lymphectomy that was not eligible for inclusion; (5) those that had pathologic types other than squamous carcinoma; (6) those who died in the perioperative period; or (7) those with tumors located at sites other than the thoracic esophagus.

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This paper was translated from Chinese into English by Guangzhou Liheng Medical Translation and edited by Hope J. Lafferty on 2009-11-16.

The Chinese version of this paper is avaiable at http://www.cjcsysu.cn/cn/article.asp?id=16282.

Received: 2009-06-22; Accepted: 2009-09-23

Clinical data

A total of 361 patients with esophageal carcinoma who underwent esophagectomy at Sun Yat-sen University Cancer Center between January 1997 and March 2004 were included in our study. There were 303 men and 58 women with ages ranging from 34 years to 82 years (median 58 years). The sites of primary tumor included: 32 in the upper thoracic esophagus, 211 at the middle thoracic esophagus, and 118 at the lower thoracic esophagus. As for the surgical approaches, 279 patients were via left thoracic approach and 82 via right thoracic approach. Lymphectomy extension included the conventional two fields. Postoperative staging were all stage III (pT3N1M0 in 320 patients; pT4N1M0 in 41 patients), and all were squamous carcinoma. There were 76 patients with highly differentiated, 166 with moderately differentiated, and 119 patients with poorly differentiated disease. Three patients received postoperative adjuvant radiochemotherapy, 48 patients received adjuvant radiotherapy, and 17 patients underwent adjuvant chemotherapy. The rest of the patients did not undergo adjuvant therapy.

Observational indices

Univariate analyses were performed for 15 indices of age, sex, tumor site, tumor length, surgical approach, surgical duration, perioperative blood transfusion, complications, ligation of the thoracic duct, depth of tumor infiltration (T staging), lymph-node metastasis, number of regions with lymph-node involvement, differentiation, adjuvant therapy, and other pathologic indices. Postoperative complications included those associated with surgery that required interventions (including cardiopulmonary complications, anastomosis leakage, wound infection, and other complications). The metastatic region was divided into the thoracic field (mediastinal field) and the abdominal field. The number of metastatic regions was defined as: 1 (either the thoracic or the abdominal region) and 2 (both the thoracic and abdominal regions). Tissue differentiations were categorized into groups of high, moderate, and low differentiations, and those with mixed degrees of differentiation were classified into the lower type. Adjuvant therapy included the intended adjuvant chemotherapy and radiotherapy.

Follow-up

The means of follow-up and data collection included regular outpatient follow-up, mailings, and telephone follow-up. Survival time was calculated in days. For deceased patients, the survival time was calculated from surgery to death; for living patients, survival time was from surgery to the last follow-up.

Statistical analysis

Data were analyzed using SPSS version 16.0. Survival analysis and univariate analysis were processed using the Kaplan-Meier method and log-rank test. The Cox proportional hazards model was used for multivariate analysis. Surviving patients and patients that died from causes other than the carcinoma were regarded as censored data. Data were recognized as statistically significant when $P < 0.05$.

Results

Follow-up

The 361 patients with stage-III esophageal carcinoma were followed to March 5, 2009, unless they died before this date. The follow-up period was 1–133 months (median 17 months). A total of 45 patients were still alive at the end of the follow-up period, and 18 patients were lost to follow-up (follow-up rate of 95.0%). Of the 298 deceased patients, 295 died from the carcinoma and 3 patients died from other causes, including 1 that died from postoperative radiotherapy and 2 that died from unknown causes.

Survival conditions

The median survival time was 18 months, and the cumulative rates of 1-, 2-, 3-, 4-, and 5-year survival were 67.7%, 40.6%, 27.5%, 23.4%, and 20.1%, respectively (Figure 1).

Univariate analysis

Univariate analysis showed that factors associated with prognosis were depth of carcinoma infiltration, lymph node metastasis, number of involved lymphatic regions, surgical complications, and operation duration. Other indices were not correlated with the prognosis (Table 1; survival curves are shown in Figures 2–7).

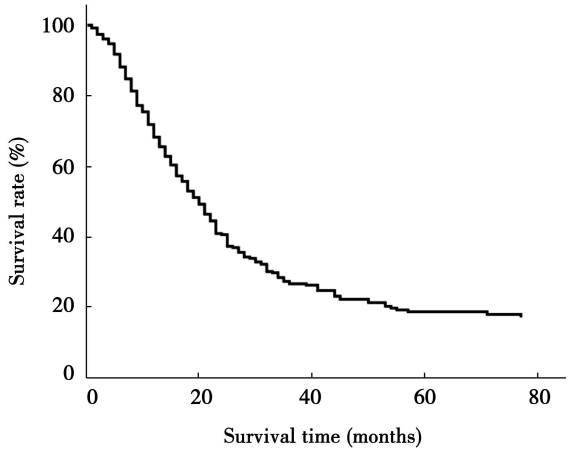

Figure 1 The overall survival curve of 361 patients with stage-III thoracic esophageal squamous carcinoma

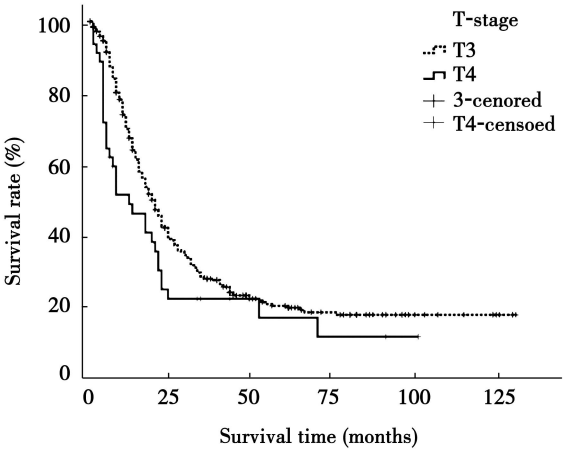

Figure 2 Survival curves of patients at different T stages

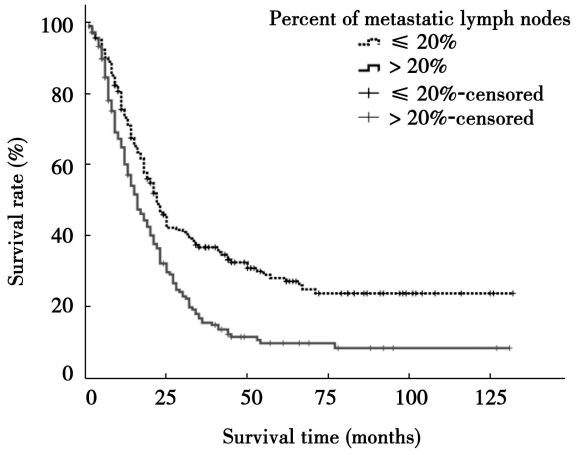

Figure 3 Survival curves of patients by percent of metastatic lymph node involvement of ≤ 20% and > 20%

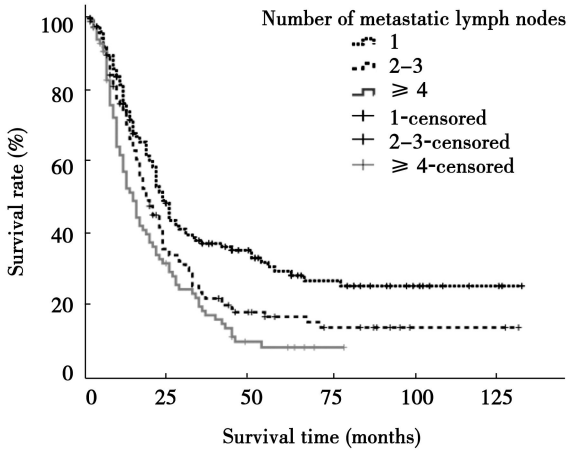

Figure 4 Survival curves of patients with different numbers of metastatic lymph nodes

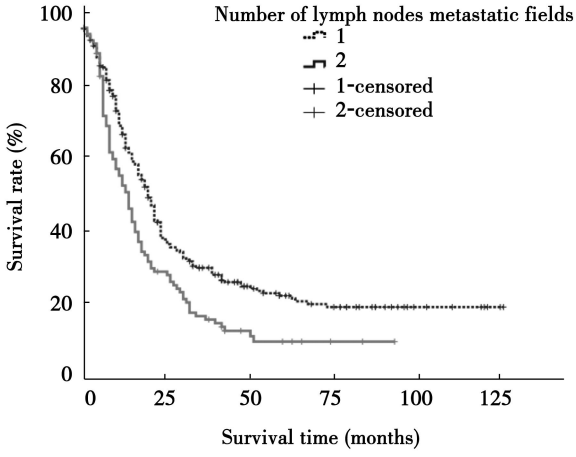

Figure 5 Survival curves of patients with different numbers of lymph node metastatic fields

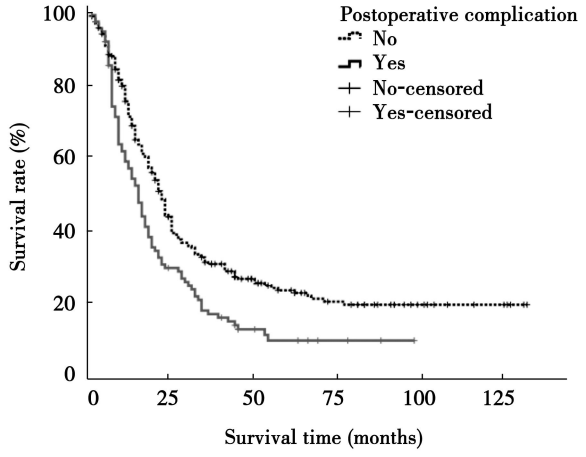

Figure 6 Survival curves of patients with or without postoperative complications

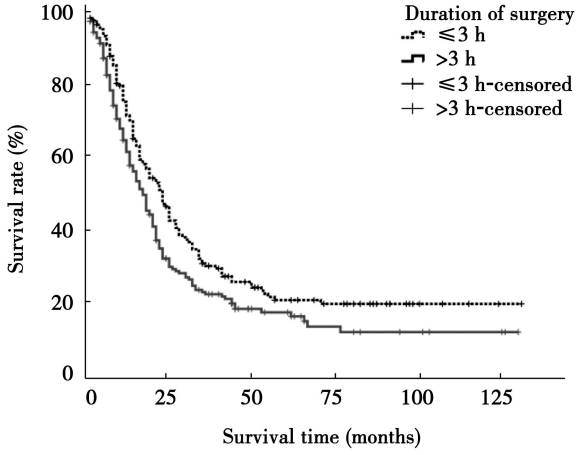

Figure 7 Survival curves of patients with durations of surgery ≤ 3 hours and > 3 hours

By stratifying the surgical complications, 90 patients had complications reported, including 36 patients with pulmonary complications, 17 with anastomosis leakage, 11 with cardiac complications, 11 with wound infection, and 15 patients with other complications. As compared with those without complications, those with pulmonary complications and anastomosis leakages had poorer prognoses (P = 0.045, X^2 = 4.023; P = 0.012, X^2 = 6.265). Patients with cardiac complications, infectious diseases, and other disorders had similar outcome to those without complications (P = 0.671, 0.328, and 0.079, respectively).

Multivariate analysis

Factors that were correlated with prognosis as analyzed by univariate analysis were introduced into the Cox model, showing that the depth of infiltration, lymph node metastasis, and surgical complications were independent predictors of prognosis (Table 2).

Table 1 Univariate survival analysis of 361 patients with stage-III thoracic esophageal squamous cell carcinoma

Variable	Patient No.	Overall survival rate (%)			*P*	χ^2
		1-year	3-year	5-year		
Gender						
Male	303	66.0	26.6	20.2	0.211	1.565
Female	58	76.8	31.9	20.7		
Age (years)						
≤60	215	68.5	28.9	21.7	0.404	0.697
>60	146	66.7	25.3	17.5		
Tumor location						
Upper thorax	27	74.6	41.1	24.9	0.339	2.161
Middle thorax	217	66.2	29.4	21.9		
Lower thorax	117	68.6	19.9	15.8		
Tumor length (cm)						
≤5	181	74.6	29.2	23.1	0.107	2.603
>5	180	60.9	25.7	16.8		
Operative approach						
Left thorax	279	68.7	28.1	20.9	0.361	0.833
Right thorax	82	64.4	25.4	17.5		
Duration of surgery (h)						
≤3	163	77.8	31.4	21.6	0.034	4.476
>3	198	62.7	24.2	19.4		
Postoperative complication						
No	271	72.0	30.6	21.8	0.004	8.377
Yes	90	54.7	18.2	15.3		
Thoracic duct ligation						
No	138	70.5	25.0	16.5	0.481	0.496
Yes	223	65.9	29.1	22.6		
Depth of invasion						
pT3	320	68.9	26.9	19.3	0.035	4.430
pT4	41	50.5	21.2	15.9		
Lymph node metastasis rate						
≤20%	183	74.1	38.4	30.0	0.000	20.542
>20%	178	61.0	16.1	10.1		
Number of metastatic lymph nodes						
1	139	76.4	38.8	30.7	0.000	18.482
2–3	130	71.1	22.6	17.2		
≥4	92	53.0	17.1	8.8		
Number of lymph node metastatic fields						
1	293	71.8	31.9	24.3	0.001	11.486
2	68	58.2	17.3	10.4		
Differentiation						
Well	76	69.6	30.6	20.3	0.589	0.019
Moderate	166	72.1	27.5	19.9		
Poor	119	64.6	24.8	19.9		
Postoperative adjuvant therapy						
No	293	66.9	29.7	22.4	0.135	2.239
Yes	68	71.3	17.5	10.2		
Perioperative transfusion						
No	299	69.1	28.6	20.6	0.202	1.629
Yes	62	61.3	22.1	17.5		

Discussion

Pathologic characteristics and prognosis

In recent years, the impact of lymph-node metastasis on outcomes for patients with esophageal carcinoma has drawn more and more attention. Although the widely used TNM staging system for esophageal carcinoma does not list the number of lymph node metastasis or the degree of metastasis, most clinical investigations show that the number of lymph-node metastasis and degree of the metastasis are independent risk factors of poor prognosis[2-6]. In the present study, we used the number of lymph node metastasis, the degree of metastasis, and the number of involved lymphatic regions to stratify the patients. These three factors were correlated with prognosis in univariate analysis. However, only the degree of lymphatic metastasis was correlated with prognosis. That may be because the contribution of the number of lymph node metastasis and involved lymphatic regions is attributable to the degree of lymphatic metastasis.

Depth of infiltration is an important part of the international staging system on esophageal carcinoma. Studies from other countries[7] showed that the rate of lymphatic metastasis is correlated with the depth of infiltration. The metastatic rate is 0 for carcinomas in situ, and metastatic rates of T1, T2, T3, and T4 are 11%, 43%, 77%, and 67%, respectively. As mentioned above, lymphatic metastasis is an independent risk factor of prognosis, and depth of infiltration is associated with lymphatic metastasis, indicating that T stage is also an important prognostic factor. In the present study, both univariate and multivariate analyses showed that T staging was an independent prognostic factor of stage-III thoracic esophageal carcinoma, which was consistent with other Chinese reports[8]. The study suggested that the prognosis of patients with deeper infiltrations was worse.

Previous studies showed that tumor differentiation was associated with prognosis. For the same pathologic types, tumors with lower differentiation are more malignant, bearing poorer outcomes[9]. But most investigations show conflicting results[10]. Our study also found that the differentiation was not significantly associated with prognosis (P = 0.200).

Surgical complications and prognosis

Studies in western countries showed that postoperative complications for patients with esophageal carcinoma were between 12.3% and 38% [11-12]. Surgical complications may markedly influence quality-of-life, or even lead to death, and may compromise patient immunity for a prolonged period. Currently, there are numerous studies focused on how to prevent and

Table 2 Multivariate survival analysis of 361 patients with stage-III thoracic esophageal squamous cell carcinoma

Parameter	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI
Lymph node metastasis rate	0.600	0.128	21.910	1	0.000	1.823	1.418–2.343
Postoperative complication	0.321	0.140	5.259	1	0.022	1.378	1.048–1.813
T-stage	0.549	0.192	8.153	1	0.004	1.732	1.188–2.526

SE, standard error; CI, confidence interval.

manage complications , while few focus on its correlation with prognosis. In our study, the survival rate of the complication-free group was significantly higher than the group with complications, and both univariate and multivariate analyses suggested a correlation between surgical complications and prognosis. The results showed that surgical complications were independent prognostic factors of outcomes for patients with stage-III esophageal carcinoma after operation. Further stratification of patients with surgical complications showed that pulmonary complications and anastomosis leakage yielded worse outcomes. However, because the number of patients in the group was small, further studies with larger sample sizes are needed.

Some studies[13-14] show that, with prolonged operation duration, the injuries are more severe, and intravenously infused low-temperature fluids lead to hypothermia. Hypothermia may delay postoperative arousal and suppress immunity, leading to severe complications. In our study, we used 3 h as the cutoff time, and the result showed that patients with surgery ⩽ 3 h had significantly longer survival times than those > 3 h (statistically significant in univariate analysis but not in multivariate analysis). In conjunction with the results of our study, we proposed that the compromised survival time by prolonged operation duration was probably due to its negative effects on surgical injury and immunity, thus increasing surgical complications. As stated before, surgical complications are important prognostic factors, and prolonged operation duration would be included in surgical complications.

Adjuvant therapy and prognosis

The role of postoperative adjuvant therapy has long been debated. Leonard *et al.*[15] thought that adjuvant chemotherapy could improve disease-free survival rates for patients with esophageal carcinoma, while not prolonging the overall survival time. However, a study from the US showed that the 2-year survival rate of an adjuvant chemotherapy group was 60%, 20% higher compared with the control group[16]. Prophylactic radiotherapy after operation can kill residual tumor cells, aiming to eradicate lesions of micrometastasis and improve local control. However, studies in the past 3 decades have not obtained definite results on the effect of prophylactic radiotherapy. Xiao *et al.*[17] proposed that postoperative radiotherapy was able to improve survival rates for patients with positive lymphatic metastasis and stage-III carcinoma, rather than for those with negative lymphatic metastasis or stage-I or stage-II carcinoma. In our study, the median survival time of the adjuvant and non-adjuvant therapy arms was not significantly different. In the first 2 years after operation, the survival rates of the two groups were similar; thereafter, the survival rate descended more rapidly in the adjuvant therapy group than in the non-adjuvant therapy group. The survival benefits of our study are different from other results, which may be due to the large age span of our patients (about 7 years) and the diversity of adjuvant regimens. In addition, patients in our study were those underwent radical esophagectomy, they can seldom benefit from adjuvant therapy which increases adverse reactions, thereby influencing long-term survival.

Other factors and prognosis

Age is generally a prognostic factor of cancer, while its role in patients with esophageal carcinoma is conflicting in various studies[4,18]. Generally speaking, because the metabolic rates of older adults are low, the malignancy and infiltrative ability of the carcinoma is not so great so that metastasis can be delayed. Esophageal carcinoma in young patients always shows poor biologic activities with enhanced infiltrative activity, and the disease progresses rapidly. Thus, survival time of older adults is longer than younger patients[18]. In the present study, patients had stage-III esophageal squamous carcinoma, so the disease was advanced. Although the infiltrative activity of carcinoma in older adults was low, their physiologic activity and immunity are so poor that the proportion of older patients that underwent adjuvant therapy was low. Their compliance with radiotherapy was also low. Therefore, the outcomes of both arms were similar.

The resection of esophageal carcinoma is closely associated with the choice of surgical access. Studies[19] show that the right thoracic access approach can ensure esophagectomies of sufficient length and thorough two-field resections compared with the left approach, though it is complex, more invasive, and has a high incidence of complications. Thus, patients that undergo right access will have more survival benefits. In our study, the survival rates of right and left access were similar, which conflicted with other reports. Patients in our study were from 5 years to 10 years ago when the option of surgical access primarily aimed at resecting the primary tumor. With respect to the scope of lymphectomy, due to the limitations of theoretical level and technical skill, the differences between the two points of access were relatively small. Thus, patients who underwent right access did not benefit from the approach.

In conclusion, the authors proposed that, among postoperative clinical and pathologic characteristics of patients with stage-III esophageal carcinoma, T stage, the degree of lymphatic metastasis, and surgical complications were independent prognostic factors.

References

[1] Shao LF, Gao ZR, Wei GQ, et al. Surgical treatment of carcinoma of the esophagus and gastric cardia: 34-year investigation [J]. Chin J Surg, 2001,39(1):44-46. [in Chinese]

[2] Tachibana M, Kinugasa S, Yoshimura H, et al. Clinical outcomes of extended esophagectomy with three-field lymph node dissection for esophageal squamous cell carcinoma [J]. Am J Surg, 2005,189 (1):98-109.

[3] Kunisaki C, Akiyama H, Nomura M, et al. Developing an appropriate staging system for esophageal carcinoma [J]. J Am Coll Surg, 2005, 201 (6):884-890.

[4] Zhang DK, Su XD, Lin P, et al. Survival analysis of patients with stage II squamous cell carcinoma of the thoracic esophagus after esophagectomy [J]. Chin J Cancer, 2008,27(2):113-118. [in Chinese]

[5] Yang L, Feng LG, Ye SD, et al. Prognostic evaluation after esophagectomy for squamous cell carcinoma of thoracic esophagus [J]. Chin J Cancer, 2000,19(11):1008-1011. [in Chinese]

[6] Wang YG, Wang LJ, Zhang QB, et al. The cancerous factors influencing the prognosis of the patients with esophagectomy [J]. Chin J Tumor, 2007,29(8):604-608. [in Chinese]

[7] Rice TW, Zuccaro G Jr, Adelstein DJ, et al. Esophageal carcinoma:depth of tumor invasion is predictive of regional lymph node status [J]. Ann

Thorac Surg, 1998,65(3):787-792.
[8] Wang YG, Wang LJ, Zhang QB, et al. The cancerous factors influencing the prognosis of the patients with esophagectomy [J]. Pract J Cancer, 2001,16(5):516-520. [in Chinese]
[9] Vansteenkiste JF, De Leyn PR, Deneffe GJ, et a1. Survival and prognostic factors in resected N2 non-small cell lung cancer:a study of 140 cases [J]. Ann Thorac Surg, 1997,63(5):1441-1450.
[10] Khan OA, Alexiou C, Soomro I, et a1. Pathological determinants of survival in node-negative oesophageal cancer [J]. Br J Surg, 2004,91(12): 1586-1591
[11] Muller JM, Erasmi H, Stelzner M, et al. Surgical therapy of esophageal carcinoma [J]. Br J Surg, 1990,77(8): 845-857.
[12] Lei C, Xi HB, Xia P, et al. The incidence and prevention of complications following radical surgery for esophageal carcinoma [J]. J Mod Oncol, 2008,16(4):572-574. [in Chinese]
[13] Huang L, Huang B, Pan LH, et al. Logistic analysis of influencing factors of delayed recovery after general anesthesia [J]. J Clin Anesthesiol, 2006,22(7):547-549. [in Chinese]
[14] Li Y, Tong H, Xiong LZ. Perioperative hypothermia after epidural anesthesia [J]. J Clin Anesthesiol, 2003,19(3):191-192. [in Chinese]
[15] Leonard GD, Reilly EM. Post-operative chemotherapy improves disease-free survival, but not overall survival in people with oesophageal squamous cell carcinoma [J]. Cancer Treat Rev, 2004,30(5)473-477.
[16] Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial [J]. Lancet, 2002,359 (9319):1727-1733.
[17] Xiao ZF, Yang ZY, Liang J, et al. Clinical value of prophylactic radiotherapy after curative resection of esophageal carcinoma [J]. Chin J Oncol, 2002,24(6):608-611. [in Chinese]
[18] Liu YZ. Clinical research of esophageal carcinoma in younger and older people [J]. J Postgraduates Med, 2004,27(8):48-49. [in Chinese]
[19] Udagawa H, Akiyama H. Surgical treatment of esophageal cancer: Tokyo experience of the three-field technique [J]. Dis Esoph, 2001,14 (2):110-114.