Original Article

Clinicopathologic factors associated with pathologic upstaging in patients clinically diagnosed stage T2N0M0 squamous cell esophageal carcinoma

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ABSTRACT

Background: Even with the use of contrast-enhanced thin-layer chest computed tomography (CT) and endoscopic ultrasonography (EUS), the likelihood of cT2N0M0 squamous cell esophageal cancer correlating with the final pathologic outcome is exceedingly low. We therefore sought to investigate the associations between different risk factors and pathologic upstaging in stage T2N0M0 esophageal cancer patients who underwent esophagectomy.

Materials and Methods: We retrospectively reviewed the clinicopathological characteristics of 224 stage T2N0M0 squamous cell esophageal cancer patients who underwent complete resection over a 2-year period (October 2016–September 2018). The tumor volume (TV) was automatically measured from thin-layer chest CT scans using imaging software. Univariate and multivariate analyses were performed to identify the risk factors associated with upstaging. A receiver operating characteristic (ROC) curve was plotted, and its ability to identify pathological upstaging was assessed.

Results: A total of 224 patients with clinical stage T2N0M0 squamous cell esophageal carcinoma (SCEC) underwent esophagectomy; of these patients, 96 (42.86%) had a more advanced stage during the final pathologic review than during the initial diagnosis. The risk factors for pathologic upstaging included a large TV, high total cholesterol (TC), high triglycerides (TGs), high platelet-to-lymphocyte ratio (PLR), and high number of lymph nodes examined. The ROC analysis demonstrated an area under the curve of 0.845 (95% confidence interval 0.794–0.895).

Conclusions: In SECC diagnosed as stage T2N0M0 by CT and EUS, the incidence of postoperative pathologic upstaging increases with a large TV, high TC, high TGs, high PLR, and high number of lymph nodes examined.

KEY WORDS: Postoperative upstage, squamous cell esophageal caicinoma, tumor volume

INTRODUCTION

Esophageal cancer is an increasingly prevalent malignant tumor with a poor prognosis. Despite improvements in diagnostic and therapeutic patterns, little progress has been made in treatment outcomes, with the median survival time increasing only by 3.2 months over the past 30 years.[1] Although the national guidelines clearly demonstrate that patients with stage T1N0M0 cancers of the esophagus and gastroesophageal junction are appropriately treated with surgery alone, disagreements in treatment selection become evident when clinicians encounter a clinical stage T2N0M0 diagnosis.[2] At this stage, patients should have node-negative disease and are thus theoretically suited for primary surgical resection alone in theory. Nonetheless, for operable patients with cT2N1-3 disease, induction therapy is an appropriate treatment option before esophagectomy.[2-4] However, the likelihood of clinical T2N0M0 correlating with the same pathologic stage is low.

Previous institutional reports have reported that even with the currently available diagnostic tools including endoscopic ultrasonography (EUS) and positron-emission tomography (PET) scanning, the accurate identification of patients with cT2N0M0 remains difficult. Undetected nodal disease was

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encountered with esophagectomy in 39%–55% of clinical T2N0M0 patients.[5,6] In addition, other studies have shown that the current techniques for preoperative staging are inaccurate in identifying early nodal metastasis, with up to 15% of cT1/T2-N0 patients having N1 disease after resection.[7] Accurate staging would allow for tailored treatment plans for high-risk node-positive cohorts, while sparing node-negative patients from potentially morbid treatments such as induction chemotherapy.

Previous studies found in American national databases such as the National Cancer Database (NCDB) found that approximately 40% of cT2N0M0 patients were administered induction therapy before esophagectomy.[8,9] However, a recent retrospective review of the NCDB found no survival benefits for cT2N0M0 patients who were administered induction therapy.[8] These findings may reflect selection biases that may hinder lymph node-upstaged patients from receiving appropriate adjuvant therapy. Therefore, we conducted a retrospective study to determine the clinicopathologic features that lead to pathologic upstaging in cT2N0M0 squamous cell esophageal cancer patients and to address the risks of lymph node metastasis. We hypothesized that by identifying the subgroup with an increased likelihood of pathologic upstaging, the use of induction therapy may be associated with an increase in overall survival (OS).

MATERIALS AND METHODS

This retrospective research was approved by the Institutional Review Board of the hospital and performed using the medical records database of the Shandong Provincial Hospital Affiliated to Shandong First Medical University. Written informed consent was provided by all patients and their families before surgery. The inclusion criteria were as follows: (1) primary esophageal cancer that was clinically classified as stage T2N0M0 squamous cell carcinoma according to the tumor-node-metastasis (TNM) classification; (2) no history of other malignant tumors; (3) no history of neoadjuvant radiotherapy or chemotherapy; and (4) cases underwent esophagectomy according to the tumor location. The individual patient demographics as well as operative and postoperative variables were extracted and used for subsequent analyses.

All patients were evaluated by physical examination, laboratory tests, endoscopy with biopsy, EUS, barium swallow examination, contrast-enhanced computed tomography (CT) scans of the chest and abdomen, and ultrasonography of the neck. Then, the tumor volume (TV) was automatically measured from the thin-layer chest CT scans using imaging software [Figures 1 and 2]. PET-CT was selectively used. The following three types of esophagectomy procedures were used, depending on the tumor location: the McKeown procedure for upper tumors, the Ivor Lewis procedure for middle tumors, and the Sweet procedure for lower tumors. Two-field (mediastinal and upper abdominal) lymphadenectomy was performed in all patients. Cervical lymphadenectomy was performed only for patients suspected to have cervical lymph node metastasis (LNM). The

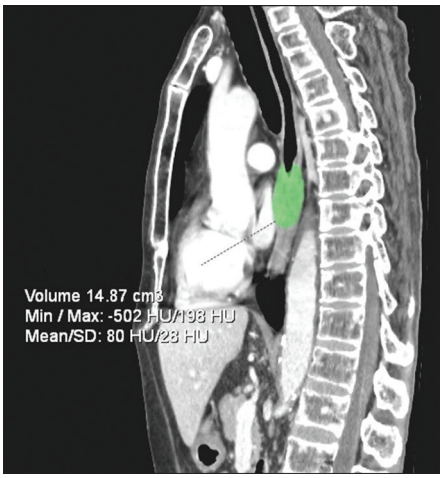

Figure 1: The reconstruction of tumor and its volume was automatically measured by software

demographic factors and pathological data including age, sex, tumor grade, lymph node status, lymphovascular invasion, number of resected lymph nodes, and proximal and distal surgical resection margins were obtained from the prospectively maintained database. Then, the esophageal tumor was staged according to the 8th ed.ition of the TNM classification of the Union for International Cancer Control and American Joint Committee on Cancer (AJCC).[10] The adequacy of lymph node dissection (LND) was examined following the recommendations for optimal LND proposed by the Worldwide Esophageal Cancer Collaboration (WECC). The WECC investigators recommended removing a minimum of 20 lymph nodes for all pT2 cancers.

Descriptive variables were expressed as the mean ± standard deviation. Categorical variables were analyzed by the Pearson Chi-square or Fisher's exact test, and continuous variables were analyzed by the sample *t*-test or Wilcoxon rank-sum test. Univariable analyses were performed to identify potential covariates associated with pathological upstaging from cT2N0M0 esophageal cancer. Then, the factors for upstaging with $P < 0.1$ from the univariate analysis were examined with multivariable logistic regression to identify the independent covariates associated with postoperative upstaging. Variables with a significant difference, $P \leq 0.05$, were eligible for inclusion in the model. To test the accuracy of each risk factor identified from the multivariable logistic regression analysis and combined effect model, a receiver operating characteristic (ROC) curve was plotted, and the area under the curve (AUC) was used to estimate the accuracy. All analyses were performed using IBM Statistical Package for the Social Sciences version 22.0 (IBM SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 224 patients were included according to the inclusion criteria. The demographics and clinical characteristics of the 224 patients are summarized in Table 1, and the postoperative pathologic characteristics are listed in Table 2. All patients

underwent R0 resection. The McKeown, Ivor Lewis, and Sweet procedures were performed in 34, 138, and 52 patients, respectively. A total of 96 patients (42.86%) were found to have significantly more severe disease after resection than their clinical stage indicated. Of these patients, 25% were upstaged due to an increase in T status alone, 31.25% were upstaged by an increase in N status alone, and the remaining 43.75% were upstaged by an increase in both T and N status. Consequently, the p-stage was IIB for 24 patients, IIIA for 32 patients, IIIB for 34 patients, and IV for 6 patients [Table 2]. No patients included in this study were found to have distant metastasis at the time of surgery. The median number of lymph nodes resected was 21.7 (range: 10–38). The lymphadenectomy was adequate in 170 patients (75.89%).

Univariate analyses were carried out to evaluate the precise value of each variable. As shown in Tables 1 and 2, the upstaged patients were more likely to be older ($P = 0.017$) and have larger TVs (4.59 cm^3 vs. 8.6 cm^3, $P = 0.02$), higher total cholesterol (TC) ($P = 0.005$), higher triglycerides (TGs) ($P < 0.001$), higher platelet counts ($P < 0.001$), and higher platelet-to-lymphocyte ratios (PLRs) ($P < 0.001$) than the patients who were not upstaged. On the postoperative pathologic scan, postoperative upstaging was significantly related to poor histological differentiation ($P = 0.018$) and a large number of lymph nodes examined (mean: 20.13 vs. 23.79, $P < 0.001$). In contrast, no significant differences in sex ($P = 0.746$), forced expiratory volume in 1 s ($P = 0.066$), body mass index ($P = 0.463$), lymphocyte count ($P = 0.433$), neutrophilic granulocyte count ($P = 0.402$), neutrophil-to-lymphocyte ratio ($P = 0.489$), smoking history ($P = 0.344$), concentration of low-density lipoprotein (LDL) ($P = 0.993$), concentration of lipoprotein (a) ($P = 0.138$), and degree of vascular lymphatic invasion ($P = 0.075$) were noted.

Furthermore, multivariate analysis using the Cox proportional-hazards model identified the following significant risk factors for pathological upstaging: TV (hazard ratio [HR]: 1.098, 95% confidence interval [CI]: 1.035–1.164, $P = 0.002$), serum TC (HR: 1.514, 95% CI: 1.095–2.093, $P = 0.012$), serum TGs (HR: 3.747, 95% CI: 2.05–6.852, $P < 0.001$), PLR (HR: 1.009, 95% CI: 1.002–1.017, $P = 0.01$), and number of lymph nodes examined (HR: 1.089, 95% CI: 1.021–1.162, $P = 0.01$). However, age, platelet counts, poor histological differentiation, operation time, and degree of vascular, lymphatic invasion did not independently influence patient upstaging in the multivariate analysis [Table 3]. Then, the variables of TV, serum TC, serum TGs, PLR, and number of lymph nodes examined were selected to create a model for postoperative upstaging. The ROC analysis [Figure 3] demonstrated an AUC of 0.845 (95% CI: 0.794–0.895). Furthermore, the AUC for TV in predicting pathologic upstaging was 0.591 (95% CI: 0.515–0.668) [Figure 4].

DISCUSSION

Even with the use of prevalent diagnostic tools, the correlation rate of cT2N0M0 squamous cell esophageal cancer with the

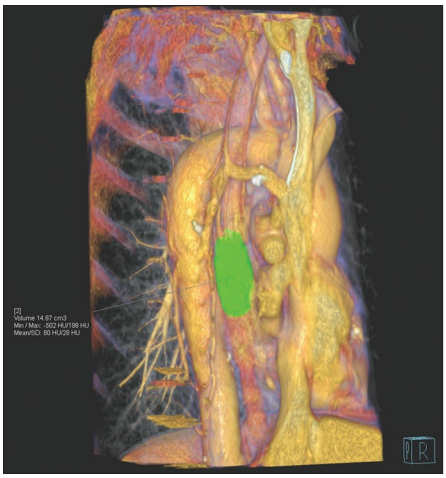

Figure 2: The reconstruction of tumor and its volume was automatically measured by software

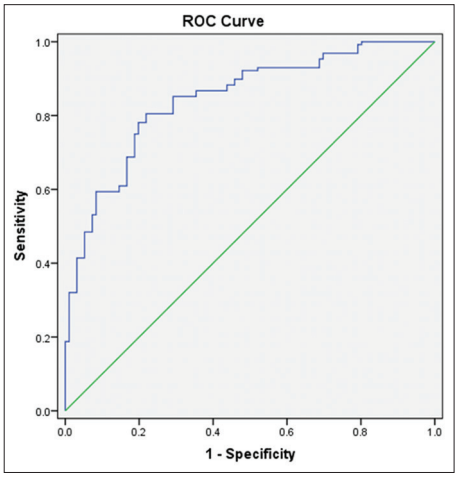

Figure 3: The receiver operating characteristic curve associated with postoperative upstaging, the area under the curve for receiver operating characteristic curve was 0.845 (95% confidence interval: 0.794–0.895)

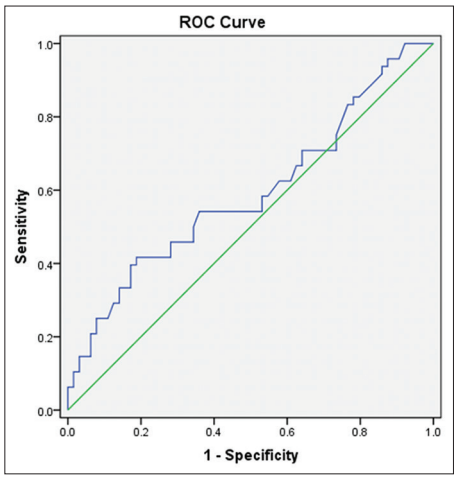

Figure 4: The area under the receiver operating characteristic curves for postoperative upstaging determined using tumor volume, the area under the curve for the receiver operating characteristic curve was 0.591 (95% confidence interval: 0.515–0.668)

Table 1: Demographics and clinical information for patients with clinical stage T2N0M0 squamous cell esophageal carcinoma that were or were not upstaged after surgical resection

Patient characteristics	Pathologic stage T2N0M0 patients *n* =128	Upstaged patients *n* =96	*P*
Age, years	61.09±7.76	57.94±10.67	0.017
Sex			0.746
Male	98	76	
Female	30	20	0.403
BMI >25 (%)	39.1	33.3	0.766
BMI >30 (%)	4.1	6.3	
Smoking history(%)	51.6	58.3	0.344
FEV1 (L)	2.74±0.64	2.86±0.72	0.066
Tumor location *n* (%)			
Upper	18 (14.1)	16(16.7)	0.707
Middle	82 (64.1)	56(58.3)	0.407
Lower	28 (21.9)	24(25)	0.633
DLCO%	87.68±14.58	86.92±19.71	0.93
BMI	24.60±3.01	23.96±3.74	0.463
Operation time(min)	258.67±77.26	233±102.83	*P*<0.001
Lymphocyte count (×10^3/μL)	1.51±0.57	1.52±0.55	0.433
Platelet counts (×10^3/μL)	210.97±61.79	263.02±88.51	*P*<0.001
Neutrophilic granulocyte counts (×10^3/μL)	5.53±3.37	5.37±3.57	0.402
Neutrophil-to-lymphocyte ratio	5.20±5.37	6.02±8.13	0.489
Platelet-to-lymphocyte ratio	147.82±46.84	217.26±182.98	*P*<0.001
Triglyceride (mmol/L)	1.16±0.57	1.75 ±0.80	*P*<0.001
Total cholesterol (mmol/L)	4.56±1.12	5±1.02	0.005
Low density lipoprotein (mmol/L)	3±1	2.94±0.92	0.993
Lipoprotein a (g/L)	0.22±0.18	0.26±0.2	0.138
D-Dimer (mg/L)	0.32±0.19	0.32±0.19	0.838
TV (cm^3)	4.59±4.59	8.60±11.53	0.02

BMI, body mass index; FEV1, forced expiratory volume in one second; TV, tumor volume; DLCO, carbon monoxide diffusing capacity.

Table 2: Pathologic characteristics of patients with clinical stage T2N0M0 squamous cell esophageal carcinoma

Patient characteristics	Pathologic stage T2N0M0 patients *n*=128	Upstaged patients *n*=96	*P*
Number of lymph nodes examined	20.13±5.19	23.79±5.51	*P*<0.001
Differentiation			
well-differentiated *n* (%)	16 (12.5)	6 (6.3)	0.173
moderately differentiated *n* (%)	94 (73.4)	64 (66.7)	0.301
poorly differentiated *n* (%)	18 (14.1)	26 (27.1)	0.018
T-factor			
T1 *n* (%)	0 (0)	0 (0)	
T2 *n* (%)	128 (100)	30 (31.3)	
T3 *n* (%)	0 (0)	60 (62.5)	
T4 *n* (%)	0 (0)	6 (6.3)	
N-factor			
N0 *n* (%)	128 (100)	24 (25)	
N1 *n* (%)	0 (0)	54 (56.3)	
N2 *n* (%)	0 (0)	18 (18.8)	
M-factor			
M0 *n* (%)	128 (100)	96 (100)	
M1 *n* (%)	0 (0)	0 (0)	
pathologic stage			
IA *n* (%)	0 (0)	0 (0)	
IB *n* (%)	0 (0)	0 (0)	
IC *n* (%)	16 (12.5)	0 (0)	
IIA *n* (%)	112 (87.5)	0 (0)	
IIB *n* (%)	0 (0)	24 (25)	
IIIA *n* (%)	0 (0)	32 (33.3)	
IIIB *n* (%)	0 (0)	34 (35.4)	
IV *n* (%)	0 (0)	6 (6.3)	
Vascular lymphatic invasion *n* (%)	6 (4.7)	11 (11.5)	0.075

final pathologic stage is exceedingly low.[11] Using the database, the major findings of this research were the following: (1) 42.86% of cT2N0M0 patients who undergo esophagectomy are pathologically upstaged and (2) of the clinicopathological variables examined in our model, the combination of TV, serum TC, serum TGs, PLR, and number of lymph nodes examined

Table 3: Multivariate analysis for the risk factors of the incidence of pathologic upstaging in clinical stage T2N0M0 squamous cell esophageal carcinoma

Parameter	β coefficient	SE	*P*	OR (95% CI)
Tumor volume	0.093	0.03	0.002	1.098(1.035-1.164)
Serum level of total cholesterol (TC)	0.415	0.165	0.012	1.514(1.095-2.093)
Serum level of triglycerides (TG)	1.321	0.308	<0.001	3.747(2.05-6.852)
Platelet-to-lymphocyte ratio	0.009	0.004	0.01	1.009(1.002-1.017)
Number of lymph nodes examined	0.085	0.033	0.01	1.089(1.021-1.162)

produced a precise model for pathologic upstaging and could help identify high-risk patients who can therefore potentially benefit from induction therapy.

The greatest tumor diameter (GTD) is an extensively used index that refers to the longest diameter of the primary tumor. Previous studies have shown that an increased GTD is an independent predictor of LNM in early esophageal cancers.[12] However, describing the true size of an irregular tumor is difficult,[13] recent progress in CT examinations has enabled doctors to precisely measure TVs.[14] Furthermore, several studies have demonstrated that prognostic correlations are stronger with TV than with GTD.[15] However, the association between TV and pathologic upstaging in T2N0M0 esophageal cancer patients who underwent complete resection has not been well discussed. Of the preoperative variables examined in our model, a large TV had a fair predictive value for pathologic upstaging and could help to identify patients with a high risk for pathologic upstaging.

The optimal number of lymph nodes to dissect has been discussed in recent years, but no consensus has been reached. The current AJCC guidelines recommend that the number of lymph nodes examined should increase with increasing pathologic T stage (10 for T1, 20 for T2, and 30 for T3 and T4).[16] Another study reported that the LNM rate was 32%, 10.6%, and 24.2% for patients who had less than 12, 12–26, and more than 26 lymph nodes dissected. When more than 12 lymph nodes were examined, the LNM rate gradually increased as the number of lymph nodes dissected increased. The differences in the extent of lymphadenectomy, pathological types, and quality of the assessments of the resected samples may cause the variability in LNM rates. In this study, the average number of lymph nodes dissected was 21.7 (range, 10–38), and the lymphadenectomy was adequate in 170 patients (75.89%). Our multivariate analysis data provided evidence that the number of lymph nodes examined has an independent role in the pathologic upstaging of T2N0M0 squamous cell esophageal cancer.

Several studies in literature have confirmed the relationship between lymphovascular invasion and LNM rate.[17,18] Tumors with lymphovascular invasion had a significantly higher risk for LNM than tumors without lymphovascular invasion. Furthermore, the presence of lymphovascular invasion also had a strong independent prognostic influence on the patients' OS and disease-free survival. The univariable analysis in this study showed that *P* value of lymphovascular invasion was 0.075, but the multivariable analysis did not confirm a distinct relationship between lymphovascular invasion rates and the incidence of pathologic upstaging, which might be related to the relatively low reported rate of lymphovascular invasion. The lymphovascular invasion rate in this group of patients was 7.59%, which is lower than that reported in a previous study (20.5%).[18]

Systemic inflammatory reactions play a significant role during all stages of tumor growth. Inflammatory reactions may contribute to tumors arising through gene mutations and epigenetic modifications.[19] The PLR is an immunological-and inflammatory-based index that has been identified as a prognostic indicator in patients with esophageal cancer.[20,21] However, the association between the PLR and postoperative pathologic upstaging has not yet been studied. We therefore conducted a study to explore the relationships between the preoperative PLR and pathologic upstaging of patients who underwent curative surgical resection for stage T2N0M0 esophageal squamous cell carcinoma. Among the clinicopathologic factors examined, the plasma PLR levels were found to be significantly correlated with postoperative upstaging.

The main component of serum TC was LDL. An increased LDL-cholesterol complex might be key to the proliferation and differentiation of malignant tumor cells. Furthermore, LDL-cholesterol has also been proven to suppress the immune system, which might enhance tumor metastasis.[22] Moreover, TGs are degraded by lipoprotein lipase to become lysophosphatidic acids (LPAs). LPAs are potent stimulators of various cellular functions related to tumor invasion and metastasis.[23] In this study, we found that preoperative serum TC and TGs were also independent risk factors for postoperative upstaging in squamous cell esophageal carcinoma (SECC) patients. This result suggests the possibility that hyperlipidemia may create favorable conditions for esophageal carcinoma cells to become invasive and metastasize to local lymph nodes.

The current research had several limitations. First, our study was retrospective and thus subjected to bias. Second, this study was conducted at a single medical center in China, and so, regional and ethnic differences were not considered. Moreover, most patients underwent two-field thoracic and abdominal lymphadenectomy, and cervical lymphadenectomy

was performed only for patients with suspected cervical LNM. Hence, the reported number of LNMs tended to underestimate the true prevalence of the nodal disease. We were further limited by our relatively small sample size, which was mainly due to the large number of patients who were excluded since they were administered neoadjuvant chemoradiation, as these therapies could significantly affect the validity of our preoperative TV measurements.

Despite these limitations, the conclusions from our analysis suggested that a large TV, high TC, high TGs, high PLR, and high number of lymph nodes examined were independent perioperative risk factors for pathologic upstaging in patients with clinical stage cT2N0M0 SECC. Furthermore, we developed and internally validated a model for pathologic upstaging. In future, further investigations involving larger study populations, randomized prospective cohorts, and practical methods from multicenter institutions should be performed to determine the optimal cutoff point with the identification of other factors associated with the pathologic upstaging of cT2N0M0 esophageal cancer.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Crane SJ, Locke GR 3rd, Harmsen WS, Zinsmeister AR, Romero Y, Talley NJ. Survival trends in patients with gastric and esophageal adenocarcinomas: A population-based study. Mayo Clin Proc 2008;83:1087-94.
2. Ajani JA, D'Amico TA, Almhanna K, Bentrem DJ, Besh S, Chao J, *et al*. Esophageal and esophagogastric junction cancers, version 1.2015. J Natl Compr Canc Netw 2015;13:194-227.
3. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, *et al*. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-84.
4. Crabtree TD, Yacoub WN, Puri V, Azar R, Zoole JB, Patterson GA, *et al*. Endoscopic ultrasound for early stage esophageal adenocarcinoma: Implications for staging and survival. Ann Thorac Surg 2011;91:1509-15.
5. Stiles BM, Mirza F, Coppolino A, Port JL, Lee PC, Paul S, *et al*. Clinical T2-T3N0M0 esophageal cancer: The risk of node positive disease. Ann Thorac Surg 2011;92:491-6.
6. Bergeron EJ, Lin J, Chang AC, Orringer MB, Reddy RM. Endoscopic ultrasound is inadequate to determine which T1/T2 esophageal tumors are candidates for endoluminal therapies. J Thorac Cardiovasc Surg 2014;147:765-71: Discussion 771-3.
7. Crabtree TD, Kosinski AS, Puri V, Burfeind W, Bharat A, Patterson GA, *et al*. Evaluation of the reliability of clinical staging of T2N0 esophageal cancer: A review of The Society of Thoracic Surgeons Database. Ann Thorac Surg 2013;96:382-90.
8. Speicher PJ, Englum BR, Ganapathi AM, Mulvihill MS, Hartwig MG, Onaitis MW, *et al*. Adjuvant chemotherapy is associated with improved survival after esophagectomy without induction therapy for node-positive adenocarcinoma. J Thorac Oncol 2015;10:181-8.
9. Yegin EG, Duman DG. Staging of esophageal and gastric cancer in 2014. Minerva Med 2014;105:391-411.
10. Rice TW, Patil DT, Blackstone EH. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: Application to clinical practice. Ann Cardiothorac Surg 2017;6:119-30.
11. Wang BY, Liu CY, Lin CH, Hsu PK, Hsu WH, Wu YC, *et al*. Endoscopic tumor length is an independent prognostic factor in esophageal squamous cell carcinoma. Ann Surg Oncol 2012;19:2149-58.
12. Suzuki C, Jacobsson H, Hatschek T, Torkzad MR, Bodén K, Eriksson-Alm Y, *et al*. Radiologic measurements of tumor response to treatment: Practical approaches and limitations. Radiographics 2008;28:329-44.
13. Zhao B, Oxnard GR, Moskowitz CS, Kris MG, Pao W, Guo P, *et al*. A pilot study of volume measurement as a method of tumor response evaluation to aid biomarker development. Clin Cancer Res 2010;16:4647-53.
14. Mozley PD, Bendtsen C, Zhao B, Schwartz LH, Thorn M, Rong Y, *et al*. Measurement of tumor volumes improves RECIST-based response assessments in advanced lung cancer. Transl Oncol 2012;5:19-25.
15. Rizk NP, Ishwaran H, Rice TW, Chen LQ, Schipper PH, Kesler KA, *et al*. Optimum lymphadenectomy for esophageal cancer. Ann Surg 2010;251:46-50.
16. Nentwich MF, von Loga K, Reeh M, Uzunoglu FG, Marx A, Izbicki JR, *et al*. Depth of submucosal tumor infiltration and its relevance in lymphatic metastasis formation for T1b squamous cell and adenocarcinomas of the esophagus, J Gastrointest Surg 2014;18:242-9.
17. Gertler R, Stein HJ, Schuster T, Rondak IC, Hofler H, Feith M. Prevalence and tomography of lymph node metastases in early esophageal and gastric cancer. Ann Surg 2014;259:96-101.
18. Lee L, Ronellenfitsch U, Hofstetter WL, Darling G, Gaiser T, Lippert C, *et al*. Predicting lymph node metastases in early esophageal adenocarcinoma using a simple scoring system. J Am Coll Surg 2013;217:191-9.
19. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140:883-99.
20. Xie X, Luo KJ, Hu Y, Wang JY, Chen J. Prognostic value of preoperative platelet-lymphocyte and neutrophil-lymphocyte ratio in patients undergoing surgery for esophageal squamous cell cancer. Dis Esophagus 2016;29:79-85.
21. Tanoglu A, Karagoz E, Yiyit N, Berber U. Is combination of neutrophil to lymphocyte ratio and platelet lymphocyte ratio a useful predictor of postoperative survival in patients with esophageal squamous cell carcinoma? Oncol Targets Ther 2014;7:433-4.
22. Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. Nat Med 2000;6:1399-402.
23. Huang MC, Graeler M, Shankar G, Spencer J, Goetzl EJ. Lysophospholipid mediators of immunity and neoplasia. Biochim Biophys Acta 2002;1582:161-7.