Available online at www.sciencedirect.com

ScienceDirect

Journal of the Chinese Medical Association 78 (2015) 229–234

www.jcma-online.com

Original Article

To evaluate the treatment response of locally advanced esophageal cancer after preoperative chemoradiotherapy by FDG-PET/CT scan

Jing-Wen Huang [a], Hui-Ling Yeh [a,*], Chung-Ping Hsu [b], Yu-Yu Lu [c], Cheng-Yen Chuang [b], Jin-Ching Lin [a], Jai-Fu Lin [a], Chen-Fa Chang [a]

[a] *Department of Radiation Oncology, Taichung Veterans General Hospital, Taichung, Taiwan, ROC*
[b] *Division of Thoracic Surgery, Taichung Veterans General Hospital, Taichung, Taiwan, ROC*
[c] *Division of Nuclear Medicine, Taichung Veterans General Hospital, Taichung, Taiwan, ROC*

Received July 4, 2014; accepted October 1, 2014

Abstract

Background: This study was designed to gauge the effectiveness of evaluation of tumor response and prognosis by positron emission tomography with 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) before and after preoperative chemoradiotherapy in patients with esophageal cancer.

Methods: Forty-nine patients from October 2008 to September 2012 with locally advanced stage esophageal carcinoma, clinical stage T2-4N0-3M0, who underwent preoperative chemoradiotherapy (preop CRT) followed by esophagectomy were enrolled in our study. All patients underwent two FDG-PET scans to compare those results with the pathologic results. Metabolic response of the primary tumor by the percentage change of the SUVmax/1 hour (ΔSUV) before and after preop CRT (ΔSUV was calculated as the difference between preop CRT SUVmax/1 hour and postop CRT SUVmax/1 hour divided by preop CRT SUVmax/1 hour at esophageal tumor) was evaluated for overall survival (OS), disease free survival (DFS), local recurrence rate, and distant failure free survival (DFFS). Prognostic factors such as age, different regimen of chemotherapy, pathologic stage, FDG-PET stage, endoscopic esophageal tumor length, and ΔSUV were analyzed. The number of highly suspect malignant lymph nodes was calculated by PET when SUVmax/1 hour $\geq$2.5 and by surgical removal. Sensitivity and specificity of regional lymph node detection by PET were also recorded.

Results: Upon univariate analysis, overall survival rate was related to ΔSUV >60% ($p = 0.045$), pathological N stage ($p = 0.001$), and endoscopic total length of esophageal tumor ($p = 0.005$). The result of FDG-PET scan after preop CRT had high specificity (96.7%) but low sensitivity (45.8%) in predicting the residual malignant lymph node numbers. The positive and the negative prediction rates were 44% and 96%, respectively. The result of the FDG-PET after preop CRT showed upstaged in 16 patients (32.6%), downstaged in nine patients (18.3%), and the same stage in 24 patients (48.9%) when compared with the pathologic stage.

Conclusion: The change of SUVmax can be a tool for evaluating tumor response after preop CRT. There is also a trend of good prognosis in overall survival rate when ΔSUV value is >60%.

Keywords: chemoradiotherapy; esophageal cancer; PET scan; preoperative; prognosis

1. Introduction

Esophageal cancer is a very menacing disease with an extremely poor prognosis because >50% of patients have unresectable disease at their first presentation in hospital.[1] Additionally, long-term survival rate was <35% even after curative surgery. Nodal involvement is the poorest prognostic

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

* Corresponding author. Dr. Hui-Ling Yeh, Department of Radiation Oncology, Taichung Veterans General Hospital, 1650, Taiwan Boulevard Section 4, Taichung 407, Taiwan, ROC.

E-mail address: hlyeh@vghtc.gov.tw (H.-L. Yeh).

http://dx.doi.org/10.1016/j.jcma.2014.11.003

factor and the survival rate drops dramatically for patients who have N2 stage or above.[2] There was also a high correlation between the pathologic nodal status and the 2- or 5-year recurrence rate.[3] Although surgery alone is still the main treatment for early stage esophageal cancer, multidisciplinary treatment typically provides a superior result for advanced disease.[4] For locally advanced esophageal cancer, preoperative chemoradiotherapy (preop CRT) followed by esophagectomy showed benefits in disease-free survival rate and local-regional control rate compared with surgery alone by a meta-analyses.[5] However, elevated 6-month treatment-related mortality was found in this group.[6] Laterza et al[7] and Adham et al[8] reported that 5-year survival rates of good responders to neoadjuvant treatment (downstaging) was 34.9−53% compared with non-responders (0−10.7%). According to these studies, the survival rate in good responders was improved by surgery but the response of chemoradiotherapy is hard to evaluate by conventional imaging, including computed tomography (CT) scans and endoscopic ultrasound. It is evident that early molecular or diagnostic markers to screen good responders after preoperative chemoradiotherapy for curative surgery are urgently needed.

Positron emission tomography (PET) using the radiolabeled glucose analogue ^{18}F-fluorodeoxyglucose (FDG) as a tracer is a functional image technique used to differentiate metabolic changes in normal cells and malignant cells. PET/CT was used for tumor staging in numerous cancers, such as colorectal, lung, breast, head and neck cancer, and malignant lymphomas.[9] Furthermore, PET/CT was an independent predictor of regional lymph node metastasis in patients with Non-small cell lung cancer (NSCLC), and it has excellent diagnostic performance for the overall assessment of distant malignancies in patients with various cancers, especially head and neck, breast, and lung cancer.[10,11] Imaging through PET/CT scan also plays an important role in monitoring early responses to neoadjuvant therapy by scrutinizing the changes of levels of the standard uptake value (SUV) of the tumor before and after the treatment.[12−14] In this study, we established a hypothesis that the changes of SUV levels after preop CRT can be used to predict the good responders for those who will obtain a benefit from the subsequent curative surgery. We also undertook analysis of the sensitivity and specificity of PET scan after preop CRT.

2. Methods

2.1. Patient population

From October 2008 to September 2012, 49 patients with locally advanced esophageal carcinoma were enrolled in this study, clinical stage T2-4N0-3M0, who underwent one of our preop CRT protocols and subsequent surgical treatment. All patients were diagnosed by biopsy via esophagoscopy. Thereafter, patients were excluded from analysis if: (1) distant metastasis was found by biopsy proven at the time of diagnosis; (2) not a candidate for curative surgery due to comorbidities or unresectable tumor; (3) other malignant disease for which they underwent treatment; or (4) poor liver or renal function which led to interruption of CRT. All patients underwent a series of preoperative staging procedures, including physical examinations, laboratory tests, ultrasound of the abdomen, a barium esophagogram, bronchoscopy, spiral CT scan of chest and abdomen, a trans-esophageal Endoscopic ultrasound (EUS), and FDG-PET/CT scanning. The above procedures were repeated after 3 weeks subsequent to completion of a preop CRT. All patients provided written informed consent. Patients who received chemotherapy with oxaliplatin instead of cisplatin were enrolled from our previous Phase II clinical trial which was approved by Institutional Review Board of Taichung Veterans General Hospital.

2.2. Chemoradiotherapy

Thirty patients received Regimen 1: cisplatin 20 mg/m^2 iv for 1 hour plus 5-FU 800 mg/m^2 continuous infusion for 24 hours daily when radiotherapy began on Day 1 to Day 4, and from Day 29 to Day 32. Nineteen patients received Regimen 2 (regimen from our Phase II clinical study with oxaliplatin): Oxaliplatin 35 mg/m^2 iv for 2 hours plus leucovorin 200 mg/m^2 iv for 2 hours and then 5-FU 400 mg/m^2 continuous infusion for 48 hours prior to radiotherapy as loading dose and then when radiotherapy starts oxaliplatin 45 mg/m^2 iv 2 hours on Day 1 of RT plus 5-FU 400 mg/m^2 continuous infusion for 24 hours on Days 1−5 of RT. On Day 15 of RT, oxaliplatin 45 mg/m^2 iv for 2 hours and then oxaliplatin 45 mg/m^2 iv for 2 hours on Day 29 of RT plus 5-FU 400 mg/m^2 continuous infusion for 24 hours on Days 29−33 of RT.

All patients underwent CT simulation in a supine position with their arms above their heads, and a customized vacuum bag was used for immobilization. The CT images were taken at a 5-mm thickness throughout the neck and the entire thorax for the upper and the middle thoracic tumors, or the entire thorax and the abdomen for the lower thoracic tumors. Gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV), and the organs at risk were outlined on the CT images. GTV is the gross tumor volume at the esophagus. CTV included GTV plus a 5 cm margin above and below the tumor, lymph nodes in the mediastinum and supraclavicular area (if the tumor was located in the upper or middle thoracic portion), and celiac trunk region (if the tumor was located in the lower thoracic portion). A margin of 0.5 cm was also added to the CTV as PTV to allow for the daily setup error and organ motion.

The IMRT plan using multiple field technique was delivered to each patient by a linear accelerator (Varian 2100EX with a 120-leaf Millennium multileaf collimator, Varian Oncology Systems, Palo Alto, CA, USA) using 6 MV photons. Dose calculations were performed using the Varian Eclipse planning system (versions 6.5−7.2.24) (Varian Medical Systems Inc., Worldwide Headquarters 3100 Hansen Way, Palo Alto, CA94304, USA) based on the pencil beam model. A total dose of 45−50.4 Gy was prescribed to the PTV in such a way that 95% of PTV was receiving 100% of the prescribed dose. The dosage constraints for organ-at-risk (OAR) were

<18Gy for mean lung dose, <20% for lung volume that receive >20Gy (V20), and <67% for heart volume that receive >45Gy (V45), and <50Gy for the total spinal cord. Radiotherapy was performed 5 days per week, with a daily dose of 180 Gy for a total course of 5–6 weeks.

2.3. Surgery

After radiation therapy was complete, surgery was performed 3–5 weeks later. The surgical procedure which was undertaken included thoracoscopic esophagectomy and esophagus reconstruction with gastric tube by laparotomy over the upper midline. The gastric tube was pushed through the retrosternal tract in the anatomic plane with the correct axis and was thereafter adequately mobilized. Besides, extended lymph node dissection including mediastinal lymph nodes (Group 2, Group 4, Group 7, Group 8, and other enlarged lymph nodes suspected to be malignant) and bilateral recurrent laryngeal lymph nodes were removed by the Chest Surgery (CS) doctor. Furthermore, radical neck lymph nodes dissection was performed by the Ear, Nose and Throat (ENT) doctor if indicated. Any abnormal operation finding such as suspected peritoneal seeding or liver metastasis was recorded and removed if possible.

2.4. Tumor regression grading

Tumor regression grade (TRG) was quantitated into five grades: TRG 1 (complete regression) showed absence of residual cancer and fibrosis extending through the different layers of the esophageal wall; TRG 2 was characterized by the presence of rare residual cancer cells scattered through the fibrosis; TRG 3 was characterized by an increase in the number of residual cancer cells, but fibrosis still predominated; TRG 4 showed residual cancer outgrowing fibrosis; and TRG 5 was characterized by an absence of regressive changes.[15] Pathological responders included TRG 1 and TRG 2, and nonresponders were TRG 3–5.

2.5. PET/CT technique

Forty-nine patients underwent PET/CT examinations which were performed on a Philips Health care Gemini TF (General Electric Advance Nxi, General Electric Medical Systems, Milwaukee, WI, USA) dedicated PET/CT system. The protocol used for the PET scan required patients to fast for 8 hours prior to the administration of ^{18}F-FDG (5 MBq/kg, up to a maximum of 550MBq), and blood glucose levels were required to be ≤150 mg/dL.^{18}F-FDG was injected into an antecubital vein, and then PET imaging was initiated after a 60-minute uptake period. PET data were reconstructed using a three-dimensional (3D) acquisition in 10–12 bed positions for 1 minute per bed. Scans were acquired from the base of the skull to the upper thighs for all patients. PET/CT images were interpreted visually plus semiqualitatively. The maximum SUV value within this was recorded as the SUVmax. Additionally, the SUVmax of preop CRT and postoperative chemoradiotherapy (postop CRT) at the primary esophageal tumor were also recorded for analysis. Lymph nodes were considered as malignant by a PET scan image when the SUV level for max/1 hour ≥2.5.[16] The cut-off value of the primary esophageal tumor varies due to postop CRT inflammation, but a single foci of elevated SUV value was be recorded and considered residual tumor. Sensitivity was defined as true positive lymph nodes (where PET showed positive findings and was proven by pathology) divided by positive pathology. Specificity was defined as true negative lymph nodes (PET showed negative findings and was proven by pathology) divided by negative pathology. The percentage of tumor downstaging or upstaging by PET was calculated.

FDG-PET/CT scan was performed prior to any treatment and 3 weeks after preop CRT. The primary tumor stage and nodal stage after preop CRT by FDG-PET scan were then analyzed by a pathologist for histopathological validation. Afterwards, a number of suspected malignant lymph nodes from the postop CRT FDG-PET/CT scan were evaluated using standard tools to arrive at the pathologic findings. Metabolic response of the primary esophageal tumor after preop CRT was assessed by ΔSUV. ΔSUV was calculated as the difference between preop CRT SUVmax/1 hour and postop CRT SUVmax/1 hour divided by preop CRT SUVmax/1 hour at the esophageal tumor. The correlation of ΔSUV between overall survival (OS), local failure free survival (LFFS), disease free survival (DFS), and distant failure free survival (DFFS) were calculated. Prognostic factors such as age, different regimen of chemotherapy, pathology stage of T, N, PET stage, endoscopic tumor length, preop CRT SUV, postop CRT SUV, and ΔSUV were also analyzed.

2.6. Statistical analysis

Kaplan–Meier curves were used to describe survival for each stage group as defined by both pathologic and FDG-PET/CT stages. We also used log-rank tests to compare the survival curves. The Cox proportional hazards regression model was used to estimate the hazard ratios and confidence intervals. A p value <0.05 was considered statistically significant. Sensitivity, specificity, positive predicted value, and negative predicted value were determined for CT, EUS-FNA, and FDG-PET/CT by using the pathology.

3. Results

Forty-nine patients (male/female ratio 48/1) with squamous cell carcinoma (95.9%) and adenocarcinoma (4.1%) were enrolled in this study. All underwent preoperative CRT including a regimen of cisplatin plus 5-FU (30 patients) or oxaliplatin plus 5-FU (19 patients) and subsequent surgical treatment. Initial tumor stage and other characteristics of the patients are described in Table 1.

Pathologic complete response (pT0N0) was 28.5% (14 patients), partial tumor response was 65.3% (32 patients), stable disease was 4% (2 patients), and progression disease was 2% (1 patient). Mean overall survival time was 17.3

Table 1
Clinical characteristics of patients.

Age (y)	
Median	53
Sex	*n*
Male	48
Female	1
Clinical stage	
T stage	
T2	1
T3	48
N stage	
N0	5
N1	28
N2	16
Histology	
Squamous cell carcinoma	47
Adenocarcinoma	2
Chemotherapy regimen	
Cisplatin+5-FU	30
Oxaliplatin+5-FU	19

months. The 3-year overall survival rate (OS), disease-free survival rate (DFS), and distant failure free survival (DFFS) were 56.8%, 55.2%, and 69.8%, respectively. The 3-year cumulative incidence rate of local recurrence was 8.8%. On univariate analysis, overall survival rate was related to ΔSUV >60% at the esophageal tumor (25 patients, 51%; $p = 0.045$; Fig. 1), pathological nodal stage after operation ($p = 0.001$), and endoscopic total length of esophageal tumor ($p = 0.005$). The group of ΔSUV >60% also showed statistical significance in disease-free survival rate ($p = 0.046$; Fig. 2), and non-significance in local recurrence rate ($p = 0.378$). Other factors such as age, different regimen of chemotherapy, pathologic T stage, pre and postop CRT PET stage, preop CRT SUV, and postop CRT SUV showed no statistical significance in OS, LC, DFS, and DFFS. On multivariate analysis, there was a statistically significant relationship in the overall survival rate with pathological nodal stage and endoscopic total length of primary tumor.

The total number of mediastinum lymph nodes that were resected was 1373. Additionally, the number of malignant lymph nodes defined by PET was 75 and benign lymph nodes

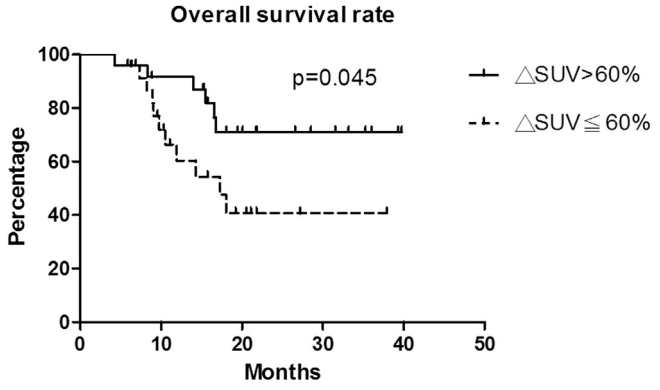

Fig. 1. Overall survival rate for ΔSUV >60% and ΔSUV ≤60%, $p = 0.045$. SUV = standard uptake value.

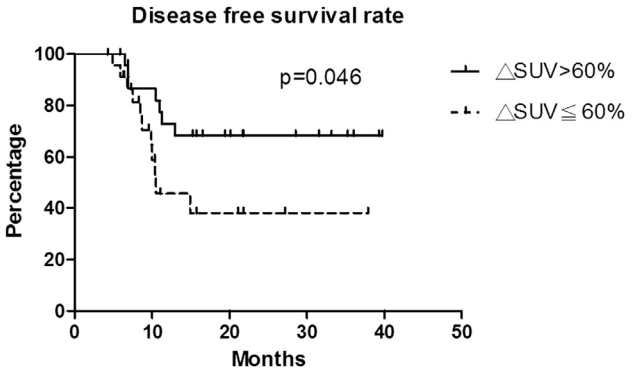

Fig. 2. Disease free survival rate for ΔSUV >60% and ΔSUV ≤60%, $p = 0.046$. SUV = standard uptake value.

was 1298 (inclusive of those lymph nodes which SUVmax <2.5 and nonmalignant proven by pathology). The specificity and sensitivity of PET/CT in predicting malignant lymph node numbers were 96.7% and 45.8%, respectively. The positive predictive value was 44% and negative predictive value was 96.9% for Nodal staging (Table 2). By comparing with PET staging after preop CRT and the actual tumor, preop results were upstaged in 16 patients (32.6%), downstaged in 9 patients (18.3%), and were the same stage in 24 patients (48.9%) by pathologic staging.

4. Discussion

Preoperative CRT followed by curative surgery gives an improved survival rate for the good tumor responder (TRG1 and TRG2). In order to best evaluate the tumor response, EUS can be used for the assessment of the extent of mucosal involvement and peritumoral nodal metastases. However, the information may be limited in cases of obstructive esophageal cancer where passage of the endoscope may not be feasible. CT scanning provides a superior assessment in regional lymphadenopathy such as mediastinum lymph nodes and metastasis disease but CT scanning is less sensitive in the detection of local regional or distant metastasis.[17] FDG-PET using the radiolabeled glucose analogue 18F-fluorodeoxyglucose (FDG) as a tracer provides a functional image of the tumor and thus can be used in tumor staging. PET combined with CT (PET/CT) provides not only functional but also

Table 2
Predictive value of nodal staging by PET.

PET	Pathology[a,b]	
	Positive	Negative
Positive	33	42
Negative	39	1259

PPV = 0.44.
NPV = 0.96.
[a] Sensitivity = 0.45 (true positive/pathology positive).
[b] Specificity = 0.96 (true negative/pathology negative).
PET = positron emission tomography; NPV = negative predictive value; PPV = positive predictive value.

morphologic information. Maximum standardized uptake value (SUVmax) is a marker of tumor glucose metabolism detected by PET/CT, which reflects the aggressiveness of tumor behavior. A meta-analysis study also used the difference of SUV to predict response, and the ΔSUV percentages ranged from 35% to 63%.[18] The result of our study showed a strong relationship between ΔSUV >60% and overall patient survival. The 3-year overall survival rate of ΔSUV >60% was 71%, and was 40.7% in the group of ΔSUV ≤60%. From our results, preop CRT with cisplatin plus 5-FU or oxaliplatin plus 5-FU seemed to be a reasonable regimen and showed slightly better survival (mean overall survival time: 17.3 months) compared with previous studies (13.3−16.8 months; INT 0113 and MRC trials). For this reason, we used ΔSUV to evaluate treatment response in this study and overall survival rate was related to ΔSUV >60% ($p = 0.045$). This data can be used to differentiate whether or not patients were responsive to chemoradiotherapy. Furthermore, the surgeon can also get information about which patients will benefit from curative surgery.[19]

Hu et al[20] showed that SUVmax had a positive correlation with tumor proliferative activity. Sun et al[21] showed that SUV max had no significant value in evaluation of prognosis of esophageal cancer by FDG-PET. Similar to Sun et al's[21] study, pre- and postop CRT absolute value of SUVmax showed no statistical significance in overall survival rate in our study. The pre- or postop CRT SUV max was still questionable in predicting the prognosis. The number and quality of studies included in each analysis might be different, which might affect the indirect comparison of results at the different PET scan time. The histology type of these studies was predominantly adenocarcinoma, which was not suitable to our region (squamous was the most frequently seen histology type, which was reflected in our study results, SCC: 95.9%). Besides, these data lacked standardization of the acquisition and processing protocols. In our study, all FDG-PET/CT were performed 3 weeks after preop CRT and standardized by the same protocol.

According to a randomized trial,[6] therapeutic strategies with or without surgery result in similar survival rates for locally advanced thoracic esophageal cancer patients (especially for patients with epidermoid tumors) responding to chemoradiation. However, another study[22] suggested that adding surgery to chemoradiotherapy improves local tumor control. But surgery does not increase the overall survival rate in this group. Our goal of improving the survival duration can be achieved by separating the good responders to preop CRT from the poor responders. In this study, using the change of SUVmax level can assist us in evaluating treatment responses.

The pathologic N stage was an important prognostic factor of overall survival rate. FDG-PET/CT can also provide information regarding the prediction of lymph node status, and it can also be an indirect tool of evaluating prognosis. We tried to use FDG-PET/CT as a noninvasive, relatively high specificity and sensitivity tool to predict who was responsive to preop CRT. In this study, preoperative PET had high specificity (96.7%) but low sensitivity (45.8%) in predicting negative malignant lymph node numbers. For this reason, there were 16 patients (32.6%) who were upstaged by PET staging. This high specificity and low sensitivity in predicting the elevated possibility of pathologic N0 if no SUVmax of lymph nodes were >2.5 implies a better survival rate for N0 than for those patients who are node positive. The sensitivity and specificity in one study by FDG-PET/CT was 63% and 100%, respectively.[23] But Cerfolio et al[23] showed that the most prevalent histology type was adenocarcinoma (85%), and that all patients had N1 disease before preop CRT. Also, the cut-off SUVmax value in that study was similar to our study (2.5). However, that study also analyzed the sensitivity and specificity of CT and EUS, which were 13% and 94%, respectively. Thus, FDG-PET/CT was a better tool in evaluating mediastinum lymph nodes.

There were several limitations for the evaluation of tumor response by FDG-PET/CT scan in our study. Firstly, physiological FDG uptake of the normal esophagus was hard to differentiate from the inflammatory esophagus after CRT. Thus, postop CRT SUVmax was defined as background FDG uptake if no significant higher uptake in single foci was found. Accordingly, there could be a bias when calculating ΔSUV. Secondly, the pre and postop CRT tumor invasion range was hard to evaluate due to the characteristics of FDG-PET. Thirdly, a low sensitivity but high specificity in detecting regional lymph nodes indicated that PET has its limitation in the detection of mediastinum lymph nodes. Fourthly, to evaluate the preop CRT N stage by PET was difficult to define due to some cluster lymph nodes which could not be precisely calculated. The ability to evaluate tumor responses after preop CRT by PET-CT thus offers another choice for those patients who will not achieve any benefit from surgery and will suffer an increased risk of mortality. For these reasons, the PET scan is a good tool for evaluating the treatment response and a good prognostic factor although some disadvantages were noted.

In conclusion, the level of ΔSUV >60% was found to be of significant predictive value for pathologic response and survival in patients with esophageal carcinoma who undergo preoperative CRT on univariate analysis. Thus, this subgroup may obtain benefits from subsequent curative surgery. Preoperative PET had a high specificity but a lack of sensitivity in the evaluation of negative pathologic node stage.

References

1. Enzinger PC, Mayer RJ. Esophageal Cancer. *N Engl J Med* 2003;**349**:2241−52.
2. Yeh HL, Hsu CP, Lin JC, Jan JS, Lin JF, Chang CF. A retrospective study of postoperative chemoradiotherapy for locally advanced esophageal squamous cell carcinoma. *Formos J Surg* 2012;**45**:172−7.
3. Xu Y, Chen Q, Yu X, Zhou X, Zheng X, Mao W. Factors influencing the risk of recurrence in patients with esophageal carcinoma treated with surgery: a single institution analysis consisting of 1002 cases. *Oncol Lett* 2013;**5**:185−90.
4. Gebski V, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *Lancet Oncol* 2007;**8**:226−34.
5. Kranzfelder M, Schuster T, Geinitz H, Friess H, Büchler P. Meta-analysis of neoadjuvant treatment modalities and definitive nonsurgical therapy for oesophageal squamous cell cancer. *Br J Surg* 2011;**98**:768−83.

6. Bedenne L, Michel P, Bouche O, Milan C, Mariette C, Conroy T, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. *J Clin Oncol* 2007;**25**:1160−8.
7. Laterza E, de' Manzoni G, Tedesco P, Guglielmi A, Verlato G, Cordiano C. Induction chemo-radiotherapy for squamous cell carcinoma of the thoracic esophagus: long-term results of a phase II study. *Ann Surg Oncol* 1999;**6**:777−84.
8. Adham M, Baulieux J, Mornex F, de La Roche de Bransat E, Ducerf C, Souquet JC, et al. Combined chemotherapy and radiotherapy followed by surgery in the treatment of patients with squamous cell carcinoma of the esophagus. *Cancer* 2000;**89**:946−54.
9. Poeppel TD, Krause BJ, Heusner TA, Boy C, Bockisch A, Antoch G. PET/CT for the staging and follow-up of patients with malignancies. *Eur J Radio* 2009;**70**:382−92.
10. Li M, Wu N, Zheng R, Liang Y, Liu Y, Zhang W, et al. Primary tumor PET/CT [^{18}F]FDG uptake is an independent predictive factor for regional lymph node metastasis in patients with nonsmall cell lung cancer. *Cancer Imaging* 2013;**12**:566−72.
11. Xu G, Zhao L, He Z. Performance of whole-body PET/CT for the detection of distant malignancies in various cancers: a systematic review and meta-analysis. *J Nucl Med* 2012;**53**:1847−54.
12. Westerterp M, van Westreenen HL, Reitsma JB, Hoekstra OS, Stoker J, Fockens P, et al. Esophageal cancer: CT, endoscopic US, and FDG PET for assessment of response to neoadjuvant therapy—systematic review. *Radiology* 2005;**236**:841−51.
13. Westerterp M, Omloo JM, Sloof GW, Hulshof MC, Hoekstra OS, Crezee H, et al. Monitoring of response to preoperative chemoradiation in combination with hyperthermia in oesophageal cancer by FDG-PET. *Int J Hyperthermia* 2006;**22**:149−60.
14. Lordick F, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. *Lancet Oncol* 2007;**8**:797−805.
15. Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer* 1994;**73**:2680−6.
16. Hellwig D, Graeter TP, Ukena D, Groeschel A, Sybrecht GW, Schaefers HJ, et al. 18F-FDG PET for mediastinal staging of lung cancer: which SUV threshold makes sense? *J Nucl Med* 2007;**48**:1761−6.
17. Barber TW, Duong CP, Leong T, Bressel M, Drummond EG, Hicks RJ. 18F-FDG PET/CT has a high impact on patient management and provides powerful prognostic stratification in the primary staging of esophageal cancer: a prospective study with mature survival data. *J Nucl Med* 2012;**53**:864−71.
18. Zhu W, Xing L, Yue J, Sun X, Sun X, Zhao H, et al. Prognostic significance of SUV on PET/CT in patients with localised oesophagogastric junction cancer receiving neoadjuvant chemotherapy/chemoradiation: a systematic review and meta-analysis. *Br J Radiol* 2012;**85**:e694−701.
19. Piessen G, Messager M, Mirabel X, Briez N, Robb WB, Adenis A, et al. Is there a role for surgery for patients with a complete clinical response after chemoradiation for esophageal cancer? An intention-to-treat case-control study. *Ann Surg* 2013;**258**:793−800.
20. Hu SL, Yang ZY, Zhou ZR, Yu XJ, Ping B, Zhang YJ. Role of SUV(max) obtained by 18F-FDG PET/CT in patients with a solitary pancreatic lesion: predicting malignant potential and proliferation. *Nucl Med Commun* 2013;**34**:533−9.
21. Sun M, Li B, Fu Z, Wei Y, Zhang J, Sun H, et al. Relationship between (18)F-fluorodeoxyglucose uptake in primary lesions and clinicopathological characteristics of esophageal squamous cell carcinoma patients. *Exp Ther Med* 2013;**5**:170−4.
22. Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol* 2005;**23**:2310−7.
23. Cerfolio RJ, Bryant AS, Ohja B, Bartolucci AA, Eloubeidi MA. The accuracy of endoscopic ultrasonography with fine-needle aspiration, integrated positron emission tomography with computed tomography, and computed tomography in restaging patients with esophageal cancer after neoadjuvant chemoradiotherapy. *J Thorac Cardiovasc Surg* 2005;**129**:1232−41.