ORIGINAL ARTICLE

Correlations of recurrence after radical surgery for esophageal cancer with glucose-lipid metabolism, insulin resistance, inflammation, stress and serum p53 expression

Liang Zheng[1]*, Jingting Jiang[2]*, Yingting Liu[2], Xiao Zheng[2], Changping Wu[3]

[1]Department of Thoracic Surgery, The Third Affiliated Hospital of Soochow University, Changzhou 213000, China; [2]Department of Tumor Biological Treatment, The Third Affiliated Hospital of Soochow University, Changzhou 213000, China; [3]Department of Oncology, The Third Affiliated Hospital of Soochow University, Changzhou 213000, China.

*These authors contributed equally to this work.

Summary

Purpose: To investigate the correlations of recurrence after radical surgery for esophageal cancer with glucose-lipid metabolism, insulin resistance, inflammation, stress and serum p53 expression.

Methods: A total of 80 patients with esophageal cancer treated in our hospital from February 2015 to October 2017 were selected and divided into two groups with 40 cases in each group. All patients enrolled underwent open radical surgery for esophageal cancer, combined with chemoradiotherapy and biotherapy after surgery, and all of them were followed up for 1 year. Postoperative recurrence, glucose-lipid metabolism, insulin resistance and inflammatory and stress responses were compared. Additionally, the serum p53 antibody index was recorded. Moreover, the relevant and independent risk factors and the correlations of postoperative recurrence time of esophageal cancer were analyzed.

Results: At 1-year follow-up after surgery, the levels of glucose-lipid metabolism indices, inflammatory factors and stress response in recurrence group were significantly higher than those in non-recurrence group (p<0.05), while the insulin resistance, the superoxide dismutase level and total antioxidant capacity in recurrence group were significantly greater than that in non-recurrence group (p<0.05). Besides, at 6-month and 1-year follow-up, the serum P53 antibody index in recurrence group was obviously higher than that in non-recurrence group (p<0.05). The complicated hypertension, hyperlipidemia and diabetes mellitus were relevant and independent risk factors for the postoperative recurrence of esophageal cancer (p<0.05). The postoperative recurrence time of esophageal cancer was negatively correlated with the levels of fasting blood glucose, total cholesterol, insulin resistance, high-sensitivity C-reactive protein and serum P53 antibody index (p<0.05), while it was positively correlated with the superoxide dismutase level (p<0.05).

Conclusions: The complicated hypertension, hyperlipidemia and diabetes mellitus are relevant and independent risk factors for the postoperative recurrence of esophageal cancer. The earlier postoperative recurrence time corresponds to the higher levels of fasting blood glucose, insulin resistance index and total cholesterol, and the stronger inflammatory and oxidative stress responses. At the same time, the changes in the p53 level have a certain guidance value in predicting the postoperative recurrence.

Key words: esophageal cancer, metabolism, insulin resistance, inflammatory response, stress response, P53 expression

Introduction

Esophageal cancer is a common malignant tumor in humans, characterized by a wide range of lesions and difficulty in treatment, involving the neck, chest and abdomen [1]. Currently, there

exists a variety of treatment methods for esophageal cancer, but surgery is still the first choice. The principle of surgical treatment is to reduce the surgical trauma, promote the recovery of patients and improve the treatment safety under the premise of ensuing the complete tumor resection and lymph node dissection [2]. The opportunity for the surgical treatment is lost for patients with postoperative recurrence and metastasis, in which case the most effective therapeutic methods are conservative interventions, such as chemotherapy, radiotherapy and biotherapy [3]. Studies have suggested that postoperative recurrence and metastasis occur within 2 years in approximately 40% of patients with esophageal cancer who underwent radical surgery [4], and there have been no standard therapeutic regimens for postoperative recurrence and metastasis of esophageal cancer yet.

With the changes in people's lifestyle, the incidence rate of esophageal cancer has shown an obvious trend for younger ages [5]. Studies have demonstrated that the risk of esophageal cancer significantly increases with the increase of age [6]. Moreover, the risks of diabetes mellitus, hyperlipidemia and other medical diseases and mutation of cancer suppressor gene p53 also increase with age. The correlations of the glucose-lipid metabolism, insulin resistance, inflammation and stress with postoperative recurrence of esophageal cancer have not been studied at present. To make up for the above deficiency, the present study aimed to evaluate the correlations of recurrence after radical surgery for esophageal cancer with glucose-lipid metabolism, insulin resistance, inflammatory and stress responses, analyze the risk factors for recurrence, and explore the predictive value of serum p53 antibody index in the recurrence of esophageal cancer.

Methods

General data

A total of 80 patients with esophageal cancer treated in our hospital from February 2015 to October 2017 were studied. The patients were 40-60 years old and all were diagnosed via biopsy. Exlusion criteria were as follows: those who were diagnosed with malignant tumor at other sites, had severe cardiopulmonary or hepatorenal dysfunction or acute respiratory infection, signed to refuse surgical treatment, had immunodeficiency or blood system infection, took immunosuppressors or received chemoradiotherapy within 90 days before enrollment. All of the patients signed informed consent, and this study was approved by the Ethics Committee of the hospital. All patients enrolled were divided into two groups (recurrence group and non-recurrence group) with 40 cases in each group using a random number table. In the non-recurrence group, there were 26 males and 14 females aged 40-60 years (mean 50.5±1.1). The duration of dysphagia was 1-8 months (mean 4.0±0.3). In the recurrence group, there were 25 males and 15 females aged 40-60 years (mean 50.6±1.0). The duration of dysphagia was 1-8 months (mean 4.1±0.3). There were no statistically significant differences in the gender, age, duration of progressive dysphagia and time of diagnosis of esophageal cancer between the two groups (p>0.05).

Observation indices

All patients enrolled underwent open radical surgery for esophageal cancer, combined with postoperative chemoradiotherapy and biotherapy, and all of them were followed up for 1 year. Postoperative recurrence, the glucose-lipid metabolism, insulin resistance, inflammation and stress responses were compared between the recurrence group and the non-recurrence group at 1 year after surgery. The variations in the serum p53 antibody index were recorded at different observation time points (before surgery, 1 month after surgery, 6 months after surgery and 1 year after surgery). Moreover, the relevant and independent risk factors for the postoperative recurrence of esophageal cancer were analyzed, and the correlations of postoperative recurrence time of esophageal cancer with the glucose-lipid metabolism indices, insulin resistance indices, inflammation-related indices, stress-related indices and serum P53 antibody index were explored.

Evaluation criteria

Determination of relevant biochemical indices: blood glucose indices including fasting blood glucose (FBG, normal reference value in adults: 3.9-6.1 mmol/L), 2-hour postprandial blood glucose (2hPBG, normal reference value in adults: ≤7.8 mmol/L) and homeostasis model assessment of insulin resistance (HOMA-IR, normal reference value in adults: 1), blood lipid indices including triglyceride (TG, normal reference value in adults: 0.56-1.71 mmol/L), total cholesterol (TC, normal reference value in adults: 2.83-5.17 mmol/L), inflammatory factors including high-sensitivity C-reactive protein (hs-CRP, normal reference value in adults: <10 mL/L), interleukin-6 (IL-6, normal reference value in adults: 0.37-0.46 ng/L) and tumor necrosis factor-α (TNF-α, normal reference value in adults: 5-100 ng/L), oxidative stress indices including malondialdehyde (MDA, normal reference value in adults: 3.52-4.78 nmol/mL), superoxide dismutase (SOD, normal reference value in adults: 0.242-0.620 μU/mL), and total antioxidant capacity in femoral venous blood (detected via FRAP, normal reference value in adults: 2.34-26.96 μU/mL). The serum p53 antibody index was detected via enzyme-linked immunosorbent assay (normal reference value: 0-10).

Statistics

SPSS 20.0 software (IBM, Armonk, NY, USA) was used for statistical processing. Measurement data, such as glucose-lipid metabolism, insulin resistance, inflammatory and stress response indices and changes in the p53 level, were expressed as mean ± standard deviation

Table 1. Comparison of glucose-lipid metabolism and insulin resistance between recurrence group and non-recurrence group

	FBG (mmol/L)	2hPBG (mmol/L)	Insulin resistance	TG (mmol/L)	TC (mmol/L)
Non-recurrence group	5.0±0.2	8.3±1.2	1.0±0.1	1.7±0.1	3.2±0.1
Recurrence group	10.6±0.8	12.4±2.3	1.3±0.1	3.9±0.2	6.2±0.3
t	42.950	9.996	13.416	62.225	60.000
p	0.000	0.000	0.000	0.000	0.000

Table 2. Inflammatory and stress responses in recurrence group and non-recurrence group

	hs-CRP (mg/L)	IL-6 (ng/L)	TNF-a (ng/L)	MDA (nmol/mL)	SOD (μU/mL)	Total antioxidant capacity (μU/mL)
Non-recurrence group	9.9±0.9	0.3±0.1	93.3±6.5	3.3±0.2	0.7±0.2	21.1±1.2
Recurrence group	17.8±2.1	1.0±0.1	241.2±11.1	6.3±0.4	0.4±0.1	9.3±0.2
t	21.869	31.305	72.720	38.184	8.485	61.345
p	0.000	0.000	0.000	0.000	0.000	0.000

(x±s). T-test was adopted for the intergroup comparison of means, and chi-square test was adopted for the intergroup comparison of rates. Univariate and multivariate logistic regression analyses were performed for the risk factors for postoperative recurrence of esophageal cancer, and Pearson's correlation analysis was also performed. P<0.05 suggested that the difference was statistically significant.

Results

Comparison of glucose-lipid metabolism and insulin resistance between the recurrence group and non-recurrence group

At 1-year follow-up after surgery, the levels of glucose-lipid metabolism indices (FBG, 2hPBG, TG and TC) in the recurrence group were all significantly higher than those in the non-recurrence group (p<0.05), and the insulin resistance in the recurrence group was significantly greater than that in the non-recurrence group (p<0.05) (Table 1).

Inflammatory and stress responses in the recurrence group and the non-recurrence group

At 1 year follow-up after surgery, the levels of inflammatory factors (hs-CRP, IL-6 and TNF-α) in the recurrence group were significantly higher than those in the non-recurrence group (p<0.05), and the level of stress response factor (MDA) in the recurrence group was also significantly higher than that in the non-recurrence group (p<0.05), while the SOD level and total antioxidant capacity in the recurrence group were significantly lower than those in the non-recurrence group (p<0.05) (Table 2).
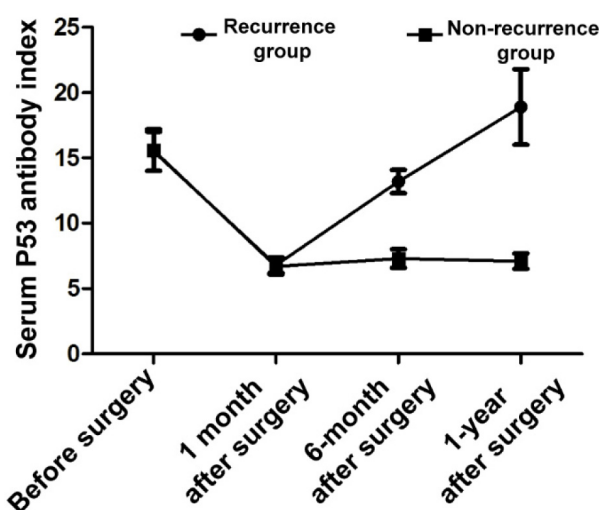
Figure 1. Variation trend of serum p53 antibody index at different observation time points. At 6-month and 1-year follow-up, the serum p53 antibody index in recurrence group is obviously higher than that in non-recurrence group (p<0.05).

Variation trend of serum p53 antibody index at different observation time points

Before surgery and at 1 month after surgery and 6-month and 1-year follow-up, the mean serum p53 antibody index was 15.6±1.6, 6.7±0.6, 7.3±0.7 and 7.1±0.6, respectively in the non-recurrence group, and 15.5±1.5, 6.8±0.6, 13.2±0.9 and 18.9±2.9 respectively in the recurrence group. It can be seen that at 6-month and 1-year follow-up, the serum p53 antibody index in the recurrence group was obviously higher than that in the non-recurrence group (t=32.727 and 25.201, p<0.05) (Figure 1).

Analysis of risk factors for postoperative recurrence of esophageal cancer

According to the univariate and multivariate logistic regression analyses of risk factors for postoperative recurrence of esophageal cancer, age above 60 years, history of smoking and drinking, complicated hypertension, hyperlipidemia and diabetes mellitus were relevant risk factors for postoperative recurrence of esophageal cancer, and complicated hypertension, hyperlipidemia and diabetes mellitus were independent risk factors for postoperative recurrence of esophageal cancer (Tables 3 and 4).

Correlation analysis of postoperative recurrence time of esophageal cancer with glucose-lipid metabolism indices, insulin resistance indices, inflammation-related indices, stress-related indices and serum p53 antibody index in the recurrence group at 1-year follow-up

The postoperative recurrence time of esophageal cancer was negatively correlated with the levels of FBG, TC, insulin resistance, hs-CRP and serum p53 antibody index (p<0.05), while it was positively correlated with the SOD level (p<0.05) (Figures 2-7).

Discussion

The most important clinical symptom of esophageal cancer is progressive dysphagia and its morbidity rate is highest in central China, especially Henan and Hebei, and it also occurs frequently in Jiangsu and Shanxi. High morbidity rates of esophageal cancer seriously affect the quality of

Table 3. Univariate analysis of risk factors for postoperative recurrence of esophageal cancer

Item	Non-recurrence group	Recurrence group	x^2	p
Gender				
Male	26	25	0.054	0.816
Female	14	15		
Age (years)				
Above 60	11	25	9.899	0.002
Within 60	29	15		
Smoking				
Yes	7	19	8.205	0.004
No	33	21		
Drinking				
Yes	8	19	6.765	0.009
No	31	21		
Complicated hypertension				
Yes	13	26	8.455	0.004
No	27	14		
Complicated hyperlipidemia				
Yes	8	25	14.907	0.000
No	32	15		
Complicated diabetes mellitus				
Yes	7	16	4.943	0.026
No	33	24		

Table 4. Multivariate logistic regression analysis of risk factors for postoperative recurrence of esophageal cancer

| Item	β	SE	W	OR	p	95%CI
Age above 60 years	0.145	0.390	0.139	0.211	0.709	0.539-2.478
Smoking	0.423	0.328	1.663	0.354	0.197	0.803-2.903
Drinking	0.328	0.371	0.982	0.281	0.459	0.619-2.624
Complicated hypertension	1.966	0.454	18.781	7.135	0.000	2.933-17.358
Complicated hyperlipidemia	1.605	0.382	17.717	4.972	0.000	2.354-10.490
Complicated diabetes mellitus	1.049	0.440	5.646	2.853	0.017	1.20-16.773

r=-0.6967,P=0.000
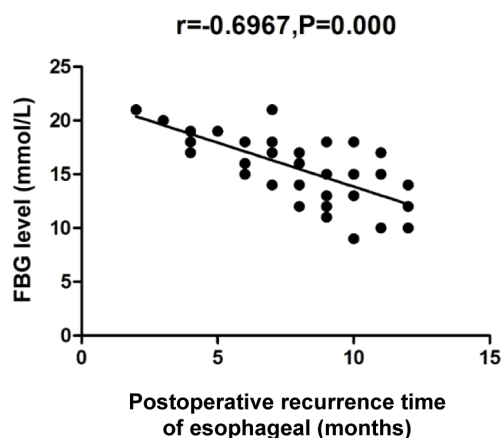
Figure 2. Correlation analysis between postoperative recurrence time of esophageal cancer and FBG level. The postoperative recurrence time of esophageal cancer is negatively correlated with the FBG level (p<0.05).
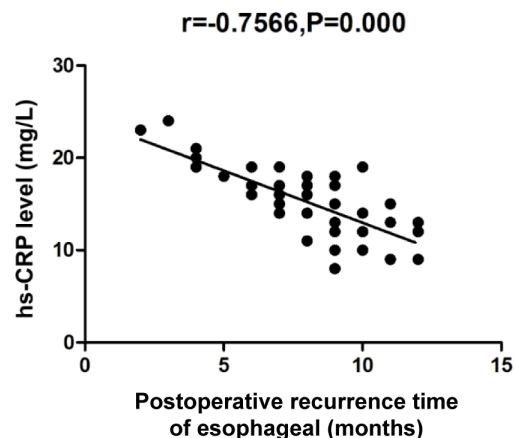
r=-0.7566,P=0.000

Figure 5. Correlation analysis between postoperative recurrence time of esophageal cancer and hs-CRP level. The postoperative recurrence time of esophageal cancer is negatively correlated with the hs-CRP level (p<0.05).
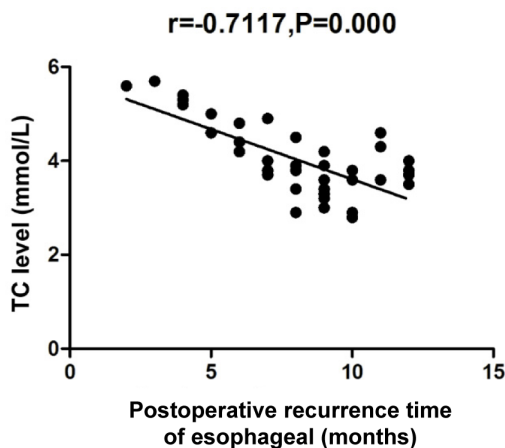
r=-0.7117,P=0.000

Figure 3. Correlation analysis between postoperative recurrence time of esophageal cancer and TC level. The postoperative recurrence time of esophageal cancer is negatively correlated with the TC level (p<0.05).
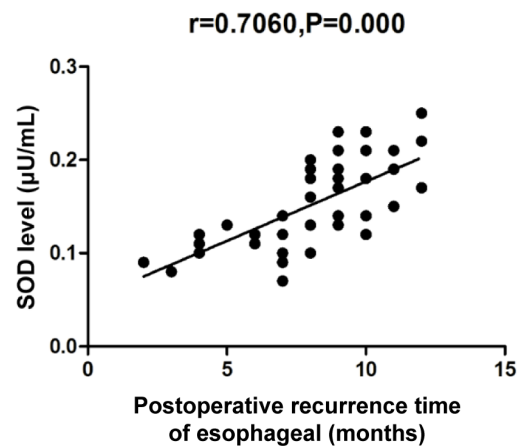
r=0.7060,P=0.000

Figure 6. Correlation analysis between postoperative recurrence time of esophageal cancer and SOD level. The postoperative recurrence time of esophageal cancer is positively correlated with the SOD level (p<0.05).
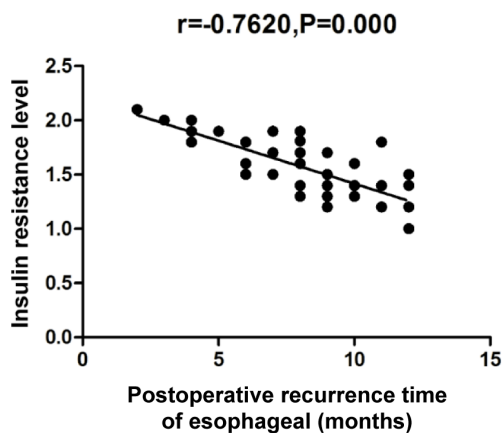
r=-0.7620,P=0.000

Figure 4. Correlation analysis between postoperative recurrence time of esophageal cancer and insulin resistance level. The postoperative recurrence time of esophageal cancer is negatively correlated with the insulin resistance level (p<0.05).
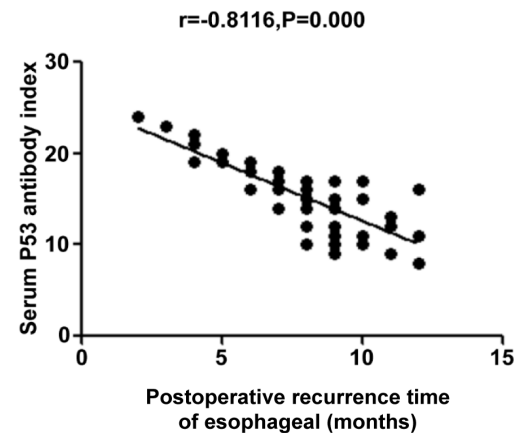
r=-0.8116,P=0.000

Figure 7. Correlation analysis between postoperative recurrence time of esophageal cancer and serum p53 antibody index. The postoperative recurrence time of esophageal cancer is negatively correlated with the serum p53 antibody index (p<0.05).

life of patients after onset, leading to emaciation and malnutrition in the early stage and tumor cachexia occurs earlier than in other malignant tumors [7]. Surgical treatment is the first therapeutic choice, but recurrences occur in more than 40% of the patients within 2 years after radical surgery of esophageal cancer [8]. A previous study [9] has suggested that the morbidity rate of esophageal cancer is positively correlated with age. Currently, more authors believe that the incidence of esophageal cancer is related to genetic factors, environmental factors and diet. With the increase of age, the risk of diabetes mellitus, hyperlipidemia and insulin resistance are significantly increased [10]. However, the correlations of glucose-lipid metabolism, insulin resistance, inflammatory and stress responses with postoperative recurrence of esophageal cancer have not been studied yet.

In the present study, the comparison of glucose-lipid metabolism, insulin resistance and inflammatory and stress responses between the recurrence group and the non-recurrence group showed that, at 1-year follow-up after surgery, the levels of glucose-lipid metabolism indices (FBG, 2hPBG, TG and TC) in the recurrence group were all significantly higher than those in the non-recurrence group, and the insulin resistance in the recurrence group was significantly greater than that in the non-recurrence group. At 1-year follow-up after surgery, the levels of inflammatory factors (hs-CRP, IL-6 and TNF-α) in the recurrence group were significantly higher than those in the non-recurrence group, and the level of stress response factor (MDA) in the recurrence group was also significantly higher than that in the non-recurrence group, while the SOD level and total antioxidant capacity in the recurrence group were significantly lower than those in the non-recurrence group, indicating that the patients with postoperative recurrence of esophageal cancer have increased blood glucose and lipid levels, insulin resistance and enhanced inflammatory and stress responses in the body. Moreover, the variation trend of serum p53 antibody index at different observation time points (before surgery, 1 month after surgery, and 6-month and 1-year follow-up) revealed that at 6-month and 1-year follow-up, the serum p53 antibody index in the recurrence group was obviously higher than that in the non-recurrence group, suggesting that the serum p53 antibody index is significantly increased in patients with postoperative recurrence of esophageal cancer. In the analysis of risk factors for postoperative recurrence of esophageal cancer it was found that the complicated hypertension, hyperlipidemia and diabetes mellitus were relevant and independent risk factors for postoperative disease recurrence.

Finally, at 1-year follow-up, the postoperative recurrence time of esophageal cancer was negatively correlated with the levels of FBG, TC, insulin resistance, hs-CRP and serum p53 antibody index, while it was positively correlated with the SOD level.

In recent years, insulin resistance has become a research hotspot in the occurrence and development of malignant tumors and evaluation of prognosis [11]. Zhang et al. [12] have confirmed hat the abnormal insulin level and abnormal glucose metabolism reduce the insulin sensitivity and result in uncontrolled cell proliferation and differentiation, thus causing malignant transformation. At the same time, the levels of lipid metabolism factors, such as G peptide, leptin [13] and adiponectin [14] will be abnormal due to the abnormal lipid metabolism, which will lead to increased activity of adipocyte-specific hormonal protein and enhanced aseptic inflammatory response in the body [15], ultimately causing malignant transformation of prostate tissue cells [16]. In addition, the p53 gene is a cancer suppressor in the normal body [17], and p53 mutation exists in more than 50% of non-small cell lung cancer and more than 80% of small cell lung cancer [18]. After p53 mutation, the p53 protein will be accumulated *in vivo*, which leads to autoimmune response in the form of target antigen [19], thereby producing the serum p53 antibody [20]. The p53 antibody index used in this study effectively reflects the p53 mutation *in vivo*.

Conclusions

The complicated hypertension, hyperlipidemia and diabetes mellitus are relevant and independent risk factors for postoperative recurrence of esophageal cancer. Earlier postoperative recurrence time corresponds to higher levels of FBG, insulin resistance index and TC, and stronger inflammatory and oxidative stress responses. At the same time, the changes in the p53 level offer a certain guidance value in predicting the postoperative recurrence.

Acknowledgements

Conflict of interests

The authors declare no conflict of interests.

References

1. Jiao W, Zhang J, Wei Y et al. MiR-139-5p regulates VEGFR and downstream signaling pathways to inhibit the development of esophageal cancer. Dig Liver Dis 2019;51:149-56.

2. Wang X, Luo Y, Li M, Yan H, Sun M, Fan T. Recurrence pattern of squamous cell carcinoma in the midthoracic esophagus: implications for the clinical target volume design of postoperative radiotherapy. Onco Targets Ther 2016;9:6021-7.

3. Tomulescu V, Stanescu C, Blajut C et al. Robotic Approach in Benign and Malignant Esophageal Tumors; A Preliminary Seven Case Series. Chirurgia (Bucur) 2018;113:202-9.

4. Harada K, Yoshida N, Baba Y et al. Pyloroplasty may reduce weight loss 1 year after esophagectomy. Dis Esophagus 2018;31:127-9.

5. Cheng Z, Geng H, Cheng Y et al. Effects of MiR-210 on proliferation, apoptosis and invasion abilities of esophageal cancer cells. JBUON 2018;23:814-9.

6. Nakajima M, Kato H, Muroi H et al. Minimally Invasive Salvage Operations for Esophageal Cancer after Definitive Chemoradiotherapy. Digestion 2018;97:64-9.

7. Belmouhand M, Svendsen LB, Kofoed SC, Normann G, Baeksgaard L, Achiam MP. Recurrence following curative intended surgery for an adenocarcinoma in the gastroesophageal junction: a retrospective study. Dis Esophagus 2018;31:136-43.

8. Kawamoto T, Nihei K, Sasai K, Karasawa K. Clinical outcomes and prognostic factors of chemoradiotherapy for postoperative lymph node recurrence of esophageal cancer. Jpn J Clin Oncol 2018;48:259-64.

9. Davies AR, Zylstra J, Baker CR et al. A comparison of the left thoracoabdominal and Ivor-Lewis esophagectomy. Dis Esophagus 2018;31:110-4.

10. Oh TK, Jeon JH, Lee JM et al. Association of high-dose postoperative opioids with recurrence risk in esophageal squamous cell carcinoma: reinterpreting ERAS protocols for long-term oncologic surgery outcomes. Dis Esophagus 2017;30:1-8.

11. van Vulpen JK, Siersema PD, van Hillegersberg R et al. Physical ExeRcise Following Esophageal Cancer Treatment (PERFECT) study: design of a randomized controlled trial. BMC Cancer 2017;17:552.

12. Zhang L, Su Y, Chen Z, Wei Z, Han W, Xu A. The prognostic value of preoperative inflammation-based prognostic scores and nutritional status for overall survival in resected patients with nonmetastatic Siewert type II/III adenocarcinoma of esophagogastric junction. Medicine (Baltimore) 2017;96:e7647.

13. Xi M, Hallemeier CL, Merrell KW et al. Recurrence Risk Stratification After Preoperative Chemoradiation of Esophageal Adenocarcinoma. Ann Surg 2018;268:289-95.

14. Mariette C, Brouquet A, Tzanis D et al. What is the impact of neoadjuvant chemoradiation on outcomes in gastro-intestinal cancer? J Visc Surg 2017;154:185-95.

15. Uno K, Koike T, Kusaka G, Takahashi Y, Ara N, Shimosegawa T. Risk of metachronous recurrence after endoscopic submucosal dissection of esophageal squamous cell carcinoma. Dis Esophagus 2017;30:1-8.

16. Zhang H, Chen X, Wang S, Fan J, Lu L. Poorer prognosis associated with simultaneous lymphatic and vascular invasion in patients with squamous carcinoma of the thoracic oesophagus. Eur J Cardiothorac Surg 2017;52:378-84.

17. Kudou K, Saeki H, Nakashima Y et al. Prognostic Significance of Sarcopenia in Patients with Esophagogastric Junction Cancer or Upper Gastric Cancer. Ann Surg Oncol 2017;24:1804-10.

18. Dong X, Sun X, Zhao X et al. The impact of intratumoral metabolic heterogeneity on postoperative recurrence and survival in resectable esophageal squamous cell carcinoma. Oncotarget 2017;8:14969-77.

19. Jingu K, Umezawa R, Yamamoto T et al. Elective nodal irradiation is not necessary in chemoradiotherapy for postoperative loco-regional recurrent esophageal cancer. Jpn J Clin Oncol 2017;47:200-5.

20. Park HC, Kim DH, Gong EJ et al. Ten-year experience of esophageal endoscopic submucosal dissection of superficial esophageal neoplasms in a single center. Korean J Intern Med 2016;31:1064-72.