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Original Research Article

Cost-effectiveness analysis of camrelizumab combination with radiotherapy for management of advanced/metastatic esophageal squamous cell carcinoma

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Abstract

Purpose: *To determine the cost-effectiveness and efficacy of camrelizumab when combined with radiotherapy in the management of advanced/metastatic esophageal squamous cell carcinoma (ESCC).*
Methods: *A retrospective analysis was carried out on clinical information of 115 patients with advanced/metastatic ESCC admitted to Huai'an Cancer Hospital between February 2017 and January 2021. Based on therapeutic modality, patients were distributed into control group (CG, 55 cases, cisplatin + paclitaxel chemotherapy) and study group (SG, 60 cases, camrelizumab + radiotherapy regimen). Clinical efficacy, adverse effects, cost indicators (total cost of treatment, out-of-pocket costs, medical insurance cost), serum tumor marker levels (CEA, CYFRA21-1, SCC-Ag), immune function (IgA, IgG, IgM), and quality of life were compared between the two groups.*
Results: *The objective remission rate (ORR) in SG (80 %) was significantly higher than in CG (61.8 %) ($p < 0.05$). Serum levels of CEA, CYFRA21-1, SCC-Ag in both groups and symptom scores decreased, while serum IgA, IgG, IgM, function, and overall quality of life score increased, but the improvement was greater in SG after 6 weeks of treatment ($p < 0.05$). Study group had significantly higher out-of-pocket expenses, health insurance costs, total costs, and cost/effectiveness than CG ($p < 0.05$).*
Conclusion: *Camrelizumab combined with radiotherapy in the treatment of advanced/metastatic ESCC is efficacious, improves immune function, reduces serum tumor marker levels, and prolongs the survival time of patients. Clinical studies using larger population should be carried out to validate the findings of this study.*

Keywords: *Cost-effectiveness, Esophageal squamous cell carcinoma, Camrelizumab, Radiotherapy, Immune function*

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INTRODUCTION

As the sixth most frequent digestive malignancy, esophageal cancer (EC) has a high morbidity and mortality rate [1]. Esophageal squamous cell carcinoma (ESCC) is the most frequent type of EC, accounting for approximately 90 % of all EC. EC is insidious and has no apparent symptoms in early stage, and some patients have mild sore throat symptoms that may be misdiagnosed as chronic pharyngitis and ignored, leading to an overall low survival rate [2,3]. Chemotherapy is

currently used in clinical trials in patients with inoperable advanced/metastatic ESCC, but outcomes are disappointing [4]. Although radical radiotherapy is one of the treatments for patients with advanced/metastatic ESCC, it has a low 3-year survival rate of only 30 - 50 % [5]. As a result, clinicians continue to face difficulties in the therapy of advanced/metastatic ESCC.

With the advancement in medical technology in recent years, bio-immunotherapy has gradually been applied to clinical therapy of patients with advanced/metastatic ESCC [6]. Camrelizumab, a home-grown PD-1 inhibitor, has shown significant benefits in treatment of various cancers [7,8]. An earlier research found that PD-1 inhibitor, camrelizumab showed good efficacy in treating intermediate-to-advanced primary hepatocellular carcinoma, and there were fewer toxic side effects [9]. There are more clinical reports on the use of camrelizumab in combination with radiotherapy for treating malignant tumors, but the cost-effectiveness of this regimen has not been fully investigated. This study investigated the efficacy and cost-effectiveness of camrelizumab and radiotherapy for advanced/metastatic ESCC, thus providing a reference for clinical treatment protocols.

METHODS

General data

A retrospective analysis was carried out on clinical information of 115 advanced/metastatic ESCC patients who were admitted in Huai'an Cancer Hospital between February 2017 and January 2021. Patients were randomly assigned to control group (CG, 55 cases receiving cisplastin + paclitaxel chemotherapy) and study group (SG, 60 cases receiving camrelizumab + radiotherapy regimen).

Inclusion criteria

Meeting the diagnostic criteria of ESCC [10] and confirmed by pathology, lesions with metastasis or clinical stage IV, complete clinical data, expected survival time > 3 months, aged between 18 - 70.

Exclusion criteria

Esophageal squamous cell carcinoma (ESCC) combined with other malignant tumors, received chemotherapy or radiotherapy before enrollment, allergic to drugs used, physically unable to tolerate chemotherapy or radiotherapy, comorbidity with serious diseases, uncontrolled hypertension, comorbidity with autoimmune diseases.

Approval was obtained from Ethics Committee of Huai'an Cancer Hospital (approval no. 2023025) and the research followed the guidelines provided in the Declaration of Helsinki [11].

Treatments

Control group (CG) was treated with cisplatin (Yunnan Biogu Pharmaceutical Co. Ltd., State Drug Quantifier H20043889) + paclitaxel (Sichuan Huiyu Pharmaceutical Co., Ltd., H20203702) chemotherapy regimen. Cisplatin 25 mg/m^2 was administered on the first day as intravenous drip, followed by 220 mg/m^2 at day 3 up to 21 days (1 chemotherapy cycle) totaling 2 cycles of chemotherapy. Study group was given camrelizumab (Suzhou Shengdian Biopharmaceutical Co, Ltd, S20190027, Suzhou, China) using a 3D conformal radiotherapy technique with CT-enhanced scans of the head and neck area, with the layer spacing set to 5 mm. The target area delineates the primary lesion and metastatic lymph node as gross tumor volume (GTV), and location of primary tumor and lymph nodes in the drainage area as the clinical target volume (CTV).

Clinical target volume (CTV) was derived by enlarging standard GTV 10 - 20 mm in the cranio-caudal direction and 5 – 8 mm in the lateral and anterior/posterior directions. Expansion on the CTV by 5 mm was applied to obtain planning target volume (PTV1 and PTV2). The portal mode was selected according to the characteristics and size of the target area. The dose of 95 % PTV1 was 50 Gy, and the dose of 95 % PTV2 was 60 Gy. The radiotherapy was performed five times weekly for 6 weeks. Additionally, camrelizumab was administered using intravenous drip, 200 mg/m^2 once every 2 weeks, for a total of 6 weeks.

Evaluation of parameters/indices

Clinical efficacy

After 6 weeks of treatment, the lesions were assessed based on WHO evaluation criteria in solid tumors, and complete disappearance of lesions was considered as complete remission (CR), lesion reduction ≥ 50 % was considered as partial remission (PR), lesion reduction < 50 % or enlargement ≤ 25 % was considered as stable disease (SD), presence of new lesions or lesion enlargement > 25 % was considered as progressive disease (PD). Objective remission rate (ORR) was calculated using Eq 1.

ORR = CR+PR …… (1)

Adverse reactions

The occurrence of leukopenia, nausea and vomiting, and radiation esophagitis during treatment was recorded in both groups.

Serum tumor marker levels

Before and after 6 weeks of treatment, 5 mL of venous blood was collected from patients in their fasted state. Samples were centrifuged at 3000 rpm for 10 min and serum refrigerated at -30 ℃. Levels of carcinoembryonic antigen (CEA), serum squamous cell carcinoma (SCC) antigen (SCC Ag), and cytokeratin 19 fragment (CYFRA21-1) were determined using electrochemiluminescence kits (Shanghai Baileigh Biotechnology Co., Shanghai, China).

Immune function

Before and after 6 weeks of treatment, immunoturbidimetric method was adopted to measure immunoglobulin (IgA, IgG, IgM) levels using kits provided by Beijing Pfei Biotechnology Co., Beijing, China.

Quality of life (QOL)

The European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) [12] was adopted to assess QOL in terms of function, overall life, and symptoms before and after 6 weeks of treatment. Scores ranged from 0 to 100 in each dimension, with high scores of functions and overall life representing good QOL, and high scores of symptoms representing poor QOL.

Cost indicators

Out-of-pocket costs, medical insurance costs, and total costs of the two groups were recorded. The cost to effect ratio was calculated, and the effect on clinical treatment was measured using ORR.

Statistical analysis

Data was analyzed with Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM, Armonk, USA). Shapiroe-Wilk test was used to determine the normal distribution of the data. The normally distributed measurement data were described by mean ± standard deviation (SD). Count data was described by rate (%) and test of significance was done using chi-square (χ^2). $P < 0.05$ was considered statistically significant.

RESULTS

Baseline data

Age, gender, lesion location, body mass index, tumor diameter, and combined metastasis were compared between the groups (Table 1) ($p > 0.05$).

Table 1: Comparison of general information

General information	Control group (n = 55)	Study group (n = 60)
Sex		
Male	33	32
Female	22	35
Age (years)	56.41±8.03	56.8±8.62
Body mass index (kg/m^2)	23.64±2.78	23.81±2.66
Lesion location		
Upper segment	13	15
Middle segment	24	30
Lower segment	18	15
Tumor diameter (cm)	11.03 ± 2.11	10.77 ± 2.37
Combined metastasis		
Yes	14	16
No	41	44

Clinical efficacy

Study group exhibited higher ORR (80 %) than CG (61.82 %) ($p < 0.05$). Thus, radiotherapy in combination with camrelizumab is efficacious compared to cisplatin + paclitaxel chemotherapy regimen in treating advanced/metastatic ESCC (Table 2).

Table 2: Comparison of clinical efficacy (n (%))

Group	CR	PR	SD	PD	Objective remission
Control (n = 55)	8 (14.55)	26 (47.27)	15 (27.27)	6 (10.91)	34 (61.82)
Study (n = 60)	15 (25.00)	33 (55.00)	9 (15.00)	3 (5.00)	48 (80.00)
χ^2					4.636
P-value					0.031

Table 3: Comparison of adverse reactions (n (%))

Group	Leukopenia	Nausea and vomiting	Radiation esophagitis	Bone marrow suppression	Total
Control (n = 55)	4 (7.27)	5 (9.09)	0	4 (7.27)	13 (23.64)
Study (n = 60)	2 (3.33)	3 (5.00)	6 (10.00)	0	11 (18.33)
χ^2					0.489
P-value					0.485

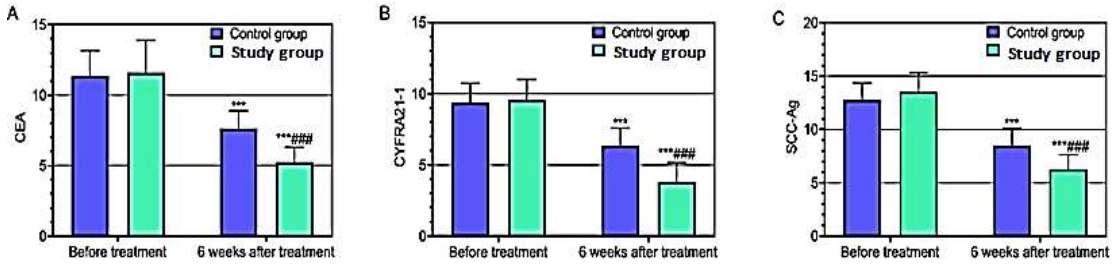

Figure 1: Comparison of serum tumor marker levels (μg/L). Shows that camrelizumab combined with radiotherapy significantly reduced serum CEA (A), CYFRA21-1 (B), and SCC-Ag (C) levels in patients with advanced or metastatic ESCC. ***P* < 0.001 compared to this group before treatment. ###*P* < 0.001, compared to control group

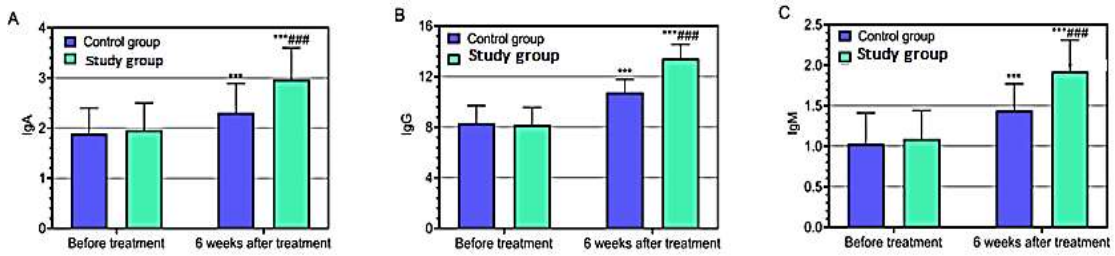

Figure 2: Comparison of immune function (g/L). Shows that camrelizumab combined with radiotherapy significantly improved IgA (A), IgG (B), and IgM (C) levels in patients with advanced or metastatic ESCC. ***P* < *0.001* compared to this group before treatment, ###*p* < *0.001* compared with control group

Adverse reactions

Study group (18.33 %) showed slightly lower incidence of adverse reactions than CG (23.64 %), with no statistical difference ($p > 0.05$). It shows that there was no increase in incidence of adverse reactions in camrelizumab and radiotherapy combination therapy (Table 3).

Serum tumor marker levels

Before treatment, both groups showed no significant differences in serum levels of CEA, CYFRA21-1 and SCC-Ag ($p > 0.05$). After 6 weeks treatment, both groups CEA, CYFRA21-1 and SCC-Ag levels significantly reduced compared to SG ($p < 0.05$) (Figure 1).

Immune function

After 6 weeks of treatment, both groups showed increased serum levels of IgA, IgG and IgM, which were much higher in study group ($p < 0.05$) (Figure 2).

Quality of life

Before treatment, both groups showed no statistically significant differences in QLQ-C30 scores for each dimension ($p > 0.05$). However, after 6 weeks of treatment, functional and overall life scores increased in both groups, while symptom scores decreased in both groups, and the improvement was greater in SG ($p < 0.05$) (Table 4).

Cost/effectiveness

Study group had higher out-of-pocket costs, health insurance costs, total costs and cost/effectiveness than CG ($p < 0.05$) (Table 5).

DISCUSSION

For the past few years, the number of patients with EC has been increasing in China, putting a heavy burden on families and society [13].

Table 4: Comparison of quality of life (mean ± SD g/L)

Group	Function		Overall life		Symptoms	
	Before treatment	After 6 weeks of treatment	Before treatment	After 6 weeks of treatment	Before treatment	After 6 weeks of treatment
Control group (n = 55)	56.75±5.34	63.38±6.73***	52.53±4.32	60.77±5.89***	70.11±6.35	61.49±5.36***
Study group (n = 60)	57.26±5.19	70.91±6.24***###	52.79±4.76	67.47±6.17***###	70.89±6.24	50.98±5.71***###

Compared with study group before treatment, ***$p < 0.001$; compare with control group, ###$p < 0.001$

Table 5: Comparison of cost effectiveness (mean ± SD)

Group	Out-of-pocket expenses (10,000 Yuan)	Medical insurance costs (million Yuan)	Total cost (million Yuan)	Cost/effectiveness (Yuan/%)
Control group (n = 55)	1.67±1.03	2.18±1.12	3.85±1.34	622.78±85.68
Study group (n = 60)	3.39±1.52	7.11±2.13	10.52±2.25	1315.25±215.36
T-value	7.039	15.327	19.095	22.278
P-value	< 0.001	< 0.001	< 0.001	< 0.001

As one of the most frequent types of EC, ESCC has complex causes and mechanisms, with genetic, dietary, living environment, chemical, and other factors all playing a role. Because of the slow onset of ESCC, majority of patients are diagnosed in mid and late period, missing out on surgical treatment and having to rely on non-surgical treatments (chemotherapy, radiotherapy, molecular targeted therapy) to extend their survival time [14-16].

In this study, patients with advanced/metastatic ESCC were treated with a combination of camrelizumab and radiotherapy, and it was found that study group exhibited higher ORR and better QOL than CG, while both groups showed no statistical difference in adverse reactions. The finding of this study is consistent with the findings of Jia Yong [17]. Thus, camrelizumab in conjunction with radiotherapy improves QOL without increasing adverse effects, while also increasing efficacy in the advanced/metastatic ESCC therapy. This study was conducted because radiotherapy causes a cytokine signaling cascade that promotes tumor antigen release and activates the immune system by killing tumor cells [18,19]. Camrelizumab is a PD-1 inhibitor that boosts T-cell activity by targeting and blocking PD-L2 and PD-L1 interactions, thereby killing tumor cells and restoring the body's immune system. It was found that both camrelizumab and radiotherapy alone had average effects, while the combination exerts a coordinated synergistic effect [20]. The reason is that combining camrelizumab with radiotherapy increases antitumor immune effect, which has radio-sensitizing properties, and therefore enhances the effect of radiotherapy, induces systemic response, and improves tumor microenvironment [21,22].

Serum tumor markers have been clinically found to be closely related to tumorigenesis and progression, among which CEA is an acidic glycoprotein that is recognized as a broad-spectrum tumor indicator [23]. The tumor marker, CYFRA21-1 is of great value in early diagnosis, efficacy and prognosis assessment of SCC patients. SCC-Ag is a specific antigen secreted primarily by squamous cells that have recently been used as an adjuvant marker for diagnosis and monitoring of malignant tumor conditions such as esophageal and lung cancers. A previous research found that EC patients showed markedly higher serum levels of CEA, CYFRA21-1, and SCC-Ag than healthy population [24]. The immune function of ESCC patients significantly reduced, and promoting immune function recovery helped to increase the anti-tumor effect and improve prognosis [25].

In this study, after 6 weeks of treatment, both groups had decreased serum levels of CEA, CYFRA21-1, and SCC-Ag, suggesting that camrelizumab in combination with radiotherapy significantly reduced serum tumor marker levels in patients with advanced/metastatic ESCC, outperforming cisplatin + paclitaxel chemotherapy regimen. Both groups had increased serum levels of IgA, IgG, and IgM, and the improvement was greater in SG, indicating that camrelizumab combined with radiotherapy is more effective than cisplatin + paclitaxel chemotherapy regimen in regulating immune function in advanced/metastatic ESCC patients. These findings suggest that camrelizumab in conjunction with radiotherapy, effectively improved patients' immune function, lowered serum tumor marker levels, inhibited disease progression, and thus promoted physical recovery in advanced/metastatic ESCC patients.

Cost-effectiveness analysis, one of the most commonly used methods in pharmaco-economics, is used to illustrate the net cost required to achieve one treatment effect by the cost to treatment effect ratio [26]. Costs in pharmacoeconomics are mainly composed of direct, indirect and hidden costs. Only drug and radiotherapy costs were counted in this study because the examination costs of patients in both groups were basically the same. This study found that SG exhibited higher out-of-pocket costs, health insurance costs, total costs and cost/effectiveness than CG. Thus, cost effectiveness of camrelizumab combined with radiotherapy regimen is higher than that of cisplatin + paclitaxel chemotherapy regimen in advanced/metastatic ESCC patients. This is attributed to the high costs of camrelizumab and radiotherapy, as well as the larger number of radiotherapies in study group, which increased cost of treatment.

Limitations of this study

There are some limitations in this research. Because this is a single-center, small-sample retrospective analysis research, certain bias may be present in the results. Furthermore, long-term survival and prognosis of advanced or metastatic ESCC treated with camrelizumab combined with radiotherapy regimens were not evaluated. At the same time, specific mechanism of action of carrilizumab combined with radiotherapy was not investigated.

CONCLUSION

Camrelizumab in combination with radiotherapy in advanced/metastatic ESCC treatment is highly efficacious, effectively improves patients' immune function and lowers serum tumor marker levels. Although, cost of camrelizumab in combination with radiotherapy is higher, it is still a more efficacious treatment option for patients with advanced/metastatic ESCC, and should be considered as one of the treatment options for patients with advanced/metastatic ESCC in the absence of other treatment options. Therefore, future clinical expansion studies should be thoroughly investigated.

DECLARATIONS

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Ethical approval

This study was approved by the Ethics Committee of Huai'an Cancer Hospital, China (approval no. 2023025).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

REFERENCES

1. *Sun Y, Wang J, Ma Y, Li J, Sun X, Zhao X, Shi X, Hu Y, Qu F, Zhang X. Radiation induces NORAD expression to promote ESCC radiotherapy resistance via EEPD1/ATR/Chk1 signalling and by inhibiting pri-miR-199a1 processing and the exosomal transfer of miR-199a-5p. J Exp Clin Canc Res 2021; 40(1): 306.*
2. *Zheng W, Yu X, Bao B. Clinical significance of peroxiredoxin 2 in esophageal squamous cell carcinoma and its role in cell proliferation and apoptosis in vitro. Trop J Pharm Res 2023; 22(7):1427-1433 doi: 10.4314/tjpr.v22i7.10*
3. *Hirata H, Niida A, Kakiuchi N, Uchi R, Sugimachi K, Masuda T, Saito T, Kageyama SI, Motomura Y, Ito S, et al. The evolving genomic landscape of esophageal squamous cell carcinoma under chemoradiotherapy. Cancer Res 2021; 81(19): 4926-4938.*
4. *Gao Y, Yang Y, Lv Y, Zhang Y, Kang M, Zhu L, Xu L, Wang F. Mortality risk factors and SOX2 and mTOR expression in patients with esophageal cancer. Cell Mol Biol 2021; 67(4): 346-357.*

5. *Li C, Zhao S, Zheng Y, Han Y, Chen X, Cheng Z, Wu Y, Feng X, Qi W, Chen K, et al. Preoperative pembrolizumab combined with chemoradiotherapy for oesophageal squamous cell carcinoma (PALACE-1). Eur J Cancer 2021; 144: 232-241.*
6. *Yu R, Wang W, Li T, Li J, Zhao K, Wang W, Liang L, Wu H, Ai T, Huang W, et al. RATIONALE 311: tislelizumab plus concurrent chemoradiotherapy for localized esophageal squamous cell carcinoma. Future Oncol 2021; 17(31): 4081-4089.*
7. *Liu J, Li J, Lin W, Shao D, Depypere L, Zhang Z, Li Z, Cui F, Du Z, Zeng Y, et al. Neoadjuvant camrelizumab plus chemotherapy for resectable, locally advanced esophageal squamous cell carcinoma (NIC-ESCC2019): A multicenter, phase 2 study. Int J Cancer 2022; 151(1): 128-137.*
8. *Lin YT, Chen Y, Liu TX, Kuang F, Huang P. Cost-effectiveness analysis of camrelizumab immunotherapy versus docetaxel or irinotecan chemotherapy as second-line therapy for advanced or metastatic esophageal squamous cell carcinoma. Cancer Manag Res 2021; 13: 8219-8230.*
9. *Xu JF, Song WC and Zheng CX. Efficacy study of domestic programmed cell death receptor 1 inhibitor carrilizumab in combination with apatinib in the first-line treatment of intermediate-stage primary hepatocellular carcinoma. China General Medicine 2022; 25: 3258-3262.*
10. *Chinese Anti-Cancer Association: The new standard for diagnosis and treatment of common malignant tumors. Beijing, China Union Medical University Press, 1999, pp. 774-786.*
11. *World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310(20): 2191-2194.*
12. *Xia D, Zhang XR, Ma YL, Zhao ZJ, Zhao R, Wang YY. Nrf2 promotes esophageal squamous cell carcinoma (ESCC) resistance to radiotherapy through the CaMKIIalpha-associated activation of autophagy. Cell Biosci 2020; 10: 90.*
13. *Yang H, Liu H, Chen Y, Zhu C, Fang W, Yu Z, Mao W, Xiang J, Han Y, Chen Z, et al. Neoadjuvant chemoradiotherapy followed by surgery versus surgery alone for locally advanced squamous cell carcinoma of the esophagus (NEOCRTEC5010): A phase III multicenter, randomized, open-label clinical trial. J Clin Oncol 2018; 36(27): 2796-2803.*
14. *Wu S, Zhang L, Deng J, Guo B, Li F, Wang Y, Wu R, Zhang S, Lu J, Zhou Y. A novel micropeptide encoded by Y-linked LINC00278 links cigarette smoking and AR signaling in male esophageal squamous cell carcinoma. Cancer Res 2020; 80(13): 2790-2803.*
15. *Zhang R, Han D, Li L, Luo W, Liu J, Qian L. EphA5 silencing increases the radiosensitivity of ESCC cells through ATM-dependent pathway. Cancer Manag Res 2020; 12: 9539-9549.*
16. *Wang H, Tang H, Fang Y, Tan L, Yin J, Shen Y, Zeng Z, Zhu J, Hou Y, Du M, et al. Morbidity and mortality of patients who underwent minimally invasive esophagectomy after neoadjuvant chemoradiotherapy vs neoadjuvant chemotherapy for locally advanced esophageal squamous cell carcinoma: A Randomized Clinical Trial. Jama Surg 2021; 156(5): 444-451.*
17. *Jia Y, Wang R. Safety and feasibility study of karilizumab in combination with radiation therapy for locally advanced esophageal squamous carcinoma. China Drugs and Clinics 2022; 22: 434-438.*
18. *Otake R, Okamura A, Yamashita K, Imamura Y, Kanamori J, Kozuki R, Takahashi K, Toihata T, Yamamoto N, Asari T, et al. Efficacy of postoperative radiotherapy in esophageal squamous cell carcinoma patients with positive circumferential resection margin. Esophagus-Tokyo 2021; 18(2): 288-295.*
19. *Lo CM, Wang YM, Chen YH, Fang FM, Huang SC, Lu HI, Li SH. The impact of radiotherapy dose in patients with locally advanced esophageal squamous cell carcinoma receiving preoperative chemoradiotherapy. Curr Oncol 2021; 28(2): 1354-1365.*
20. *Xu P, Zhang Y, Ge F, Zhang F, He X, Gao X. Modulation of tumor microenvironment to enhance radiotherapy efficacy in esophageal squamous cell carcinoma by inhibiting carbonic anhydrase IX. Front Oncol 2021; 11: 637252.*
21. *Liao XY, Liu CY, He JF, Wang LS, Zhang T. Combination of checkpoint inhibitors with radiotherapy in esophageal squamous cell carcinoma treatment: A novel strategy. Oncol Lett 2019; 18(5): 5011-5021.*
22. *Zhang W, Zhao J, Han W, Zhang H, Wang X, Li C, Chen J, Wang X, Zhao Y, Qiao X, et al. Dose escalation of 3D radiotherapy is effective for esophageal squamous cell carcinoma: a multicenter retrospective analysis (3JECROG R-03). Ann Transl Med 2020; 8(18): 1140.*
23. *Er P, Qian D, Zhang W, Zhang B, Wei H, Zhang T, Chen X, Wang Y, Zhao J, Wang Q, et al. The expression of PDGF-BB predicts curative effect in locally advanced esophageal squamous cell carcinoma treated by radiotherapy. Aging (Albany NY) 2020; 12(8): 6586-6599.*
24. *Gao L, Ji Y, Wang L, He M, Yang X, Qiu Y, Sun X, Ji Z, Yang G, Zhang J, et al. Suppression of esophageal squamous cell carcinoma development by mechanosensitive protein piezo1 downregulation. Acs Omega 2021; 6(15): 10196-10206.*
25. *Shi J, Fu C, Su X, Feng S, Wang S. Ultrasound-stimulated microbubbles inhibit aggressive phenotypes and promotes radiosensitivity of esophageal squamous cell carcinoma. Bioengineered 2021; 12(1): 3000-3013.*
26. *Gao X, Zhang R, Lei Z, Guo X, Yang Y, Tian J, Huang L. Efficacy, safety, and pharmacoeconomics of sivelestat sodium in the treatment of septic acute respiratory distress syndrome: a retrospective cohort study. Ann Palliat Med 2021; 10(11): 11910-11917.*