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RESEARCH ARTICLE

DIAGNOSE AND TREATMENT OF HYPOPHARYNGEAL CANCER WITH PRIMARY CANCER OF UPPER DIGESTIVE TRACT AT SAME TIME

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ABSTRACT

To analyze the characteristics and diagnosis of hypopharyngeal and esophageal double primary cancer and explore the treatment strategy of hypopharyngeal and esophageal (1,2) double primary cancer. We collected and analyzed n= 49 patients with hypopharyngeal and esophageal double primary cancer. The total number of patients was 49. There are male and female patients. N=47 male, N=2, female, and they are all diagnosed with hypopharyngeal esophageal double primary Synchronous cancer. 18 are younger than age <55, 18 were about 55-65, 13 were over age> 65. The clinical data of patients with hypopharyngeal and esophageal double primary cancer from February 2017 to September 2019, these patients came to our department of Otorhinolaryngology in qilu hospital of Shandong university .for the first time because of pharyngeal disease, after we find hypopharyngeal cancer, esophageal cancer found by performing a gastroscopy, we collected to date of patients (n=49), in Qilu hospital were retrospectively analyzed data, Including the auxiliary examination method, gastroscopy examination all patient showed no symptoms of esophageal discomfort, among 17 cases were evaluated for hypopharyngeal tumor who could not preserve laryngeal function total laryngectomy total esophagus, resection, and total tubular gastric replacement, was performed, in all 17 cases. There were 5 cases of hypopharyngeal and esophageal resection with preserving laryngeal cancer were used. There a clinical-stage of esophageal cancer was used minimally invasive surgery under gastroscopy. There were 8 cases of hypopharyngeal carcinoma resection with laryngeal function preservation and gastroscopic esophageal lesion. Endoscopic submucosal dissection, ESD was used. The remaining 19 cases were treated with radiotherapy. Due to physical tolerance, there was not perform a surgical operation. There were 5 cases of death due to postoperative complications of the liver and lung metastasis. for the long term treatment and the follow up was about 37 months, there is a classification of pathological and the survival.

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INTRODUCTION

Synchronous multiple primary cancer or second primary cancer refers to two or more malignant tumors occurring in the same organ of a patient with different organs, at the same time, and the growth time or interval time is less than six months, Hypopharyngeal carcinoma (hypopharyngeal carcinoma) is a malignant tumor occurring in the hypopharynx. Squamous cell carcinoma (SCC) is the most common malignant tumor in the hypopharyngeal region. The various synchronous of double primary cancer squamous cell carcinoma (SCC) is commonly caused by excessive alcohol and tobacco consumption. Its most frequently associated with hypopharyngeal and esophageal double primary cancer. The early symptoms of hypopharyngeal carcinoma are not obvious.

And It is difficult to treat; however, hypopharyngeal carcinoma because of its late detection stage. The incidence of concurrent esophageal cancer is 7.2% - 41% in domestic and foreign literature. At present, domestic and foreign literature think that one case is mainly reported, with more patients and a few clinical studies. From February 2017 to septembe2020, the clinical and pathological characteristics, diagnosis, selection of internal and external treatment methods, and treatment effect of these patients are reported.

MATERIAL AND METHODS

Clinical Material: 49 patients were admitted to the department of otolaryngology in qilu hospital, cheeloo

College of medicine, qilu hospital, Shandong University. From February 2017 to December 2019, the clinical stage, pathological classification, treatment, and follow-up were collected. Among the patients, there were n=47 male and female=2 with an average age of 50 _ 65 years, and the median age is (65) range, is (55_75). The patients had a long history of smoking and drinking. According to the AJCC and UICC in 2009, the patients had a long-term history of smoking and drinking. According to the staging criteria of pharyngeal cancer and the 2010 AJCC (7th Edition), the stages of hypopharyngeal carcinoma and esophageal carcinoma were as follows: hypopharyngeal carcinoma, stage I, n=1 in stage II n=17, stage III,n=21 and stage IV;n=10 the stage esophageal cancer was stage I, n=17 stage II n=12, and stage III, n= 20 of esophageal cancer; and pathological classification: hypopharyngeal carcinoma in situ, poorly differentiated squamous cell carcinoma, moderately differentiated squamous cell carcinoma and highly differentiated squamous cell carcinoma There were cases of esophageal carcinoma in situ, poorly differentiated squamous cell carcinoma, moderately differentiated squamous cell carcinoma and well-differentiated squamous cell carcinoma.

Methods

All the patients were diagnosed as rescuing hypopharyngeal squamous cell carcinoma by routine blood and urine examination, liver and kidney function, chest smear, electrocardiogram, barium meal gastroscopy examination, laryngoscopy examination, abdominal B-ultrasound, head and neck enhanced CT examination, and histological examination. All patients received preoperative or postoperative adjuvant radiotherapy, and chemotherapy, MRI or PET-CT examination found abnormalities, and finally, accurate diagnosis by histology or cytology. We perform a gastroscopy during preoperative hypopharyngeal esophageal double primary cancer, and it's a selective screening test for the patient of hypopharyngeal _ esophageal cancer's most reliable screening. Most of the patients who were diagnosed were not even complaining of esophageal cancer. Some of them did not have symptoms. The 17 patients have performed surgery with a total laryngectomy, total esophageal resection, and gastric tubular replacement were used. 8 cases were performed with laryngeal function preservation, gastroscopic esophageal lesion resection (ESD). The remaining 19 cases were treated with radiotherapy, chemotherapy due to late-stage and physical intolerance for not good operation. There were 5 cases of death due to postoperative complications by liver metastasis and lung metastasis. 8 cases were lost to follow up by telephone and calculated as death. The follow up including medical records, outpatient reexamination, and other means. The survival time was calculated from the date of hypopharyngeal cancer surgery to the patient's death or the last follow-up. The follow-up time was 37 months, .and the average follows up 19.4. the survival patient was 36, and the survival rate was 49%.

Three statistical analysis: SPSS grief. 23.00 software was used for statistical analysis. The continuous change was expressed as mean \pm standard deviation if it was consistent with normal distribution, and was expressed as median if it did not conform to normal distribution Log Rank (Mantel-Cox) test was used for measurement, Kaplan Meier method was used for calculation of survival rate, and the log-rank test was used for survival rate, According to the above systematic calculation, P <, 0.05 was considered to be statistically significant.

RESULTS

49 patients were analyzed, and the overall 3-years survival rate of all patients was 49%. Patients were followed up for 3 years, with a median age (65) 55_75). The longest follow-up time was 37 months. Of the patients, there were 5 cases of death due to postoperative complications by liver metastasis and lung metastasis, 17 Cases of local hypopharyngeal recurrence of a lymph node metastasis. Were performed total laryngectomy and total esophagus resection and gastric tubular replacement, 8 with resection and preserve laryngeal function and perform gastroesophageal lesion resection (ESD). There was dysphagia and With reflux after eating. Synchronous patients with multiple primary cancer are (6) associated with alcohol. Tobacco consumption, and screening patients of synchronous hypopharyngeal esophageal double primary cancer, are significant.

A reason to perform a gastroscopy during preoperative of hypopharyngeal esophageal double primary cancer, and its a selective screening test, for every one suspected with hypopharyngeal esophageal double primary cancer, in this study we found that the incidence of hypopharyngeal esophageal cancer is silent and patient doesn't develop any symptoms until we found screening gastroscopy evaluation. 40 patients had a history of 50g/d, where the other 9 patients had a history of consumption of <50g/d. The prognosis of MPC is poor because of the late finding of cancer and cancer's clinical stage. a 49 patient was followed up for 3 Years, 5patients have died, and the average follow-up is 19.4 there were 8 Cases lost to follow up and calculated as death. And the survival rate was 49 %.

Statistical analysis result

Table 1.Clinical characteristics of patients

Variable,	No. of patients	p-value
		<0.05
Sex		
Male	47	
Female	2	
Age, years		
<55	18	
55-65	18	
>65	13	
Alcohol consumption		
>50 g/d	40	
<50 g/d	9	
Hypopharyngeal cancer staging		
I	1	
II	17	
III	21	
IV	10	
Esophageal cancer staging		
I	17	
II	12	
III	20	
treatment method		
Total Throat Total Esophagus Resection and Gastric Replacement Esophagus	17	
Hypopharyngeal resection + ESD under gastroscop	8	
Hypopharyngeal resection + esophageal cancer resection	5	
Chemotherapy	19	

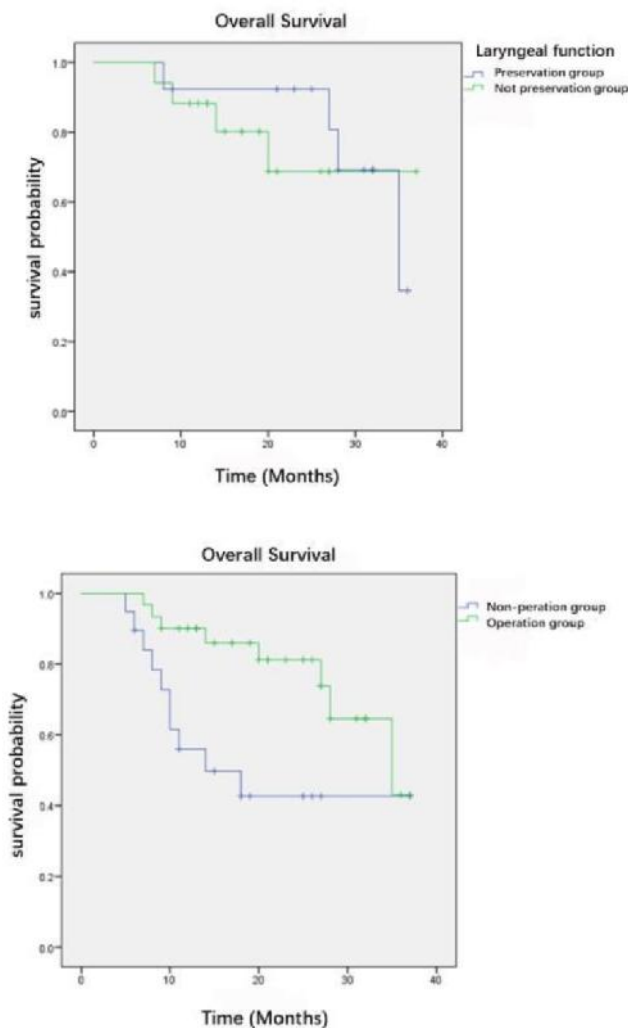


Figure 1. and figure 2. survival curve of all synchronous and esophageal cancer patients

survival curve is different, $P < 0.05$). There is no significant difference between total laryngoresection and another laryngo-sparing surgery $P > 0.05$. The significance of these curve is a surgical treatment is better than radiotherapy and chemotherapy alone.

Kaplan Meier method was used for the overall survival rate. $P=0.734$.

Survival: 3 years survival patients were 49% and 44%, respectively. the 3-year survival rates were 67%.

DISCUSSION

The pathogenesis of (3)MPC in the hypopharyngeal thoracic esophagus and the pathogenesis of MPC are still controversial. Some scholars believe that MPC is caused by micro metastasis. Cancer cells transfer to other parts through carriers (such as saliva), and sometimes their progenitor cells migrate into the epithelium. Some others think that the multicentric origin of the tumor is the possible pathogenesis of MPC, According to the theory, there are multiple cancer susceptibility centers in normal people. When the patients are exposed to different cancer factors, the time, location, and type of cancer changes are slightly different, which leads to different parts, different phases, and different types of MPC.

Hypopharynx and esophagus belong to the upper digestive tract, and mucosa is exposed to tobacco and alcohol for a long time, which leads to the chronic stimulation of cancer factors, When one site changes, the possibility of MPC in another is increased. This is the so-called theory of regional carcinogenesis of the digestive tract. The existence of this jumping focus may be one of the biological characteristics of hypopharyngeal esophageal cancer. When encountering hypopharyngeal cancer, head and neck surgeons must have the awareness of excluding esophageal MPC. The diagnosis of MPC in the hypopharyngeal and thoracic esophagus, combined with barium meal examination, endoscopy, and CT examination, will undoubtedly greatly improve the detection rate of MPC in the hypopharyngeal thoracic esophagus. Hypopharyngeal cancer is usually found in the middle and late-stage because of its atypical and nonspecific symptoms, This is also the main reason why the overall treatment effect of hypopharyngeal cancer is not good. Patients with symptoms such as throat discomfort, pharyngeal foreign body sensation, sore throat, and dysphagia should be routinely examined by an electronic laryngoscope. Not only can the lesions appear early, but also the nature of the lesions can be determined. After the diagnosis of hypopharyngeal cancer, the awareness of defining or excluding esophageal MPC should be emphasized, Esophageal barium meal examination and gastroscopy should be performed routinely. Esophageal barium meal examination can show the location of lesions in the esophagus and the relationship between extraesophageal lesions and esophagus and can be observed dynamically,

However, it is difficult to detect some small lesions and mucosal microstructural abnormalities. Gastroscopy can help us to find out the small lesions that are not easy to appear by esophagography. However, endoscopy has limitations: if the disease changes to cause obvious stenosis of the esophagus or hypopharyngeal cancer invading the esophagus, it is difficult to pass the endoscopy and can not show the distal lesions. It can be seen that both have advantages and disadvantages, The use and value of MRI and CT in the diagnosis of hypopharyngeal and thoracic esophageal carcinoma mainly lies in the understanding of the invasion of the lesion to the surrounding area, the extent of the tumor and the relationship with the surrounding important structures. For patients with hypopharyngeal carcinoma who may be suspected to exist in thoracic esophageal MPC, routine application of the above-mentioned auxiliary examination methods should be included in the comprehensive diagnosis, This not only can improve the detection rate of MPC, reduce missed diagnosis, but also can relieve the degree of lesions in the whole face, and provide a more reliable basis for the formulation of the clinical. the treatment plan.

There is a principle difference between the treatment of MPC in the hypopharyngeal and thoracic esophagus and the treatment of cancer. hypopharyngeal cancer metastasis to esophageal cancer cannot preserve the laryngeal function, total laryngectomy, total esophageal reduction, total gastric tube. esophageal cancer resection will require a thoracotomy (7), gastroscopic esophageal lesion resection (ESD), were used postoperative adjuvant radiotherapy, and chemotherapy. The treatment is difficulty because of presenting typical advanced disease, poor prognosis, or poor general health problems, or severe nutrition deficiency. In the former treatment, radical resection should be considered in the treatment of MPC at the same time, and then only one radical resection is needed, Total

hypopharyngeal total esophagectomy and gastroesophageal anastomosis can achieve simultaneous root treatment of two cancer foci, so it should be listed as the first choice. Total hypopharyngeal total tubular resection can see more complete resection of the tumor and the second undetected esophageal lesion. The choice of gastroesophageal anastomosis as the preferred reconstruction method after MPC resection of the hypopharyngeal thoracic esophagus also has the following advantages: (1) reliable blood supply of the stomach, The possibility of necrosis is very small; (2) there is only one anastomotic stoma, and the hand method is relatively simple; (3) the success rate of swallowing after the operation is high, even if the tumor recurrence, the feeding function is often not significantly hindered, which improves the quality of life of patients. Some scholars also advocate that colon replacement of esophagus should be used as the reconstruction method of feeding tube after total hypopharyngeal resection, However, the application of colon in esophageal has(8) some disadvantages compared with that of the stomach, such as it does not conform to the physiological characteristics, easy to pollute the surgical field, postoperative infection or colon necrosis and pharyngeal fistula and other complications. In addition, the operation is complex and the mortality rate is high. Two anastomotic stomas need to be made in the abdominal cavity and abdominal cavity, and the probability of anastomotic stenosis is higher than that of the pharyngeal gastric anastomosis.

There are two methods of total hypopharyngeal total esophagectomy and gastrosophageal anastomosis: (1) nonthoracostomy stripping operation is suitable for hypopharyngeal cancer, the lower limit of which is limited to the cervical esophagus, the muscular layer of thoracic esophagus is basically normal, and there is no lymph node in the upper mediastinum. (2) thoracotomy esophagectomy is suitable for the lower boundary of hypopharyngeal cancer invading the esophagus beyond the lower edge of the second thoracic vertebra, It is suspected that the esophageal muscle layer of thoracic esophageal cancer is infiltrated, and some people have found lymph node metastasis in the upper mediastinum. The advantage of this method is that it can be performed simultaneously with mediastinal lymphadenectomy, which can completely remove the cancer cells' focus. The disadvantages of this operation are that the thoracotomy has great trauma and more complications. Although this kind of simultaneous hypopharyngeal and thoracic esophageal MPC is relatively rare in clinical practice, head and neck surgeons should attach great importance to the simultaneous MPC of the hypopharynx and thoracic esophagus, and adopt various auxiliary examination methods to make clear the diagnosis and avoid missed diagnosis. Total hypopharyngeal total esophagectomy and gastroesophageal anastomosis is the first choice for hypopharyngeal and thoracic esophageal simultaneous MPC, and the therapeutic effect is good, However, prevention and treatment of complications should be put in the first place. In addition, patients without voice function after total laryngectomy will reduce the quality of life of patients to a certain extent, which should be paid attention to. The prognosis of MPC, has been affected by many factors, among which the location, pathological type, and malignant degree are relatively important. MPC is located in the external part of the head, and the tumor staging is relatively late, and the prognosis of high malignant degree is relatively poor. The difference after the intervention of simultaneous MPC may be related to the increased difficulty in the treatment of multiple

tumors. Because both hypopharyngeal cancer and esophageal cancer belong to the same category. Synchronous multiple primary carcinomas (SMPC) is two or more tumors that occur independently in the same or different sites. Hypopharyngeal neck squamous cell is the most common site of the second primary carcinoma of head cancer. This study found that hypopharyngeal carcinoma stage III and above accounted for 33%, esophageal cancer stage I Cases, accounting for 66%, hypopharyngeal cancer was mainly advanced lesions, and the esophagus was mostly in the early stage of the disease. Domestic and foreign literature reported that the hypopharyngeal esophagus had more than one hypopharyngeal carcinoma For primary cancer, early esophageal cancer in stage I-II accounted for 49.5% and hypopharyngeal lesions in stage II-IV accounted for 24%, which was similar to our findings. Patients often diagnosed with synchronous esophageal cancer by hypopharyngeal discomfort. Hypopharyngeal cancer was hidden, and the symptoms appeared later, and the clinical staging was later. Most of the esophageal cancer had no clinical manifestations. It was used to make hypopharyngeal cancer locally advanced, while esophageal cancer was mostly early Period.

The risk of MPC in hypopharyngeal cancer is higher than that in other tumors. The probability of MPC in hypopharyngeal cancer patients is 10% - 30%, and the probability of heterochronous MPC in five years is 34.4%. Hypopharyngeal cancer often invades the cervical esophagus,(9) but hypopharyngeal cancer combined with esophageal(4) MPC is rare. 49 patients with hypopharyngeal cancer were followed up for at least three years, The proportion of MPC from the esophagus was the highest (18.8%), which was much higher than that in other parts of the head (3.8%). The incidence of simultaneous hypopharyngeal esophageal MPC was 6.7%.

The treatment of hypopharyngeal and esophageal multiple primary carcinoma has not been clearly recognized. Synchronous chemoradiotherapy and surgery have been reported that 36 patients with head and neck tumors combined with concurrent hypopharyngeal cancer underwent chemoradiotherapy, and those with recurrence or residual tumor underwent salvage surgery. The three-year and five-year survival rates of 36 patients were 49% and 44%, respectively Two patients developed pharyngeal fistula after simultaneous resection of head and neck tumors with concurrent esophageal cancer, and the 3-year and 5-year survival rates were 67%. Niwa *et al.* (5), reported that 9 patients with an incomplete response or local recurrence after chemoradiotherapy underwent total pharynx and total resection of a feeding tube from 2010 to 2014 and 2 patients died within 3 months The incidence rate of the disease was 89%. According to the literature study of head and neck tumors combined with simultaneous multiple primary cancers, it was found that the survival time and complications of concurrent chemoradiotherapy plus salvage surgery were shorter than that of simple surgery. The resection range of hypopharyngeal and esophageal multiple primary carcinomas included larynx, hypopharynx, esophagus, and other important organs. Whether the patients can retain the laryngeal function and whether the same resection of hypopharyngeal and esophageal lesions can be used At present, there is no unified guideline for the treatment of this kind of disease in the world. The literature on the simultaneous multiple primary cancer mainly composed of hypopharyngeal cancer and esophageal cancer, it is mainly reported, and the number of clinical research cases is small.

Conclusion

Patients with hypopharyngeal cancer are prone to develop (10) simultaneous esophageal cancer. It is of great significance for early detection of multiple primary cancers to screen patients with hypopharyngeal cancer and esophageal cancer. A stratified treatment strategy takes into account the treatment and clinical stages of two kinds of single primary cancer to achieve a holistic treatment, which can be considered as the choice of clinical treatment. Synchronous patient need to be regularly need to do a routine examination of endoscopy, laryngoscopy should closely follow up, at frequently time interval for better and early detection in synchronous at the same time, In addition, the treatment of this multiple primary cancer is still under exploration, in this study, -we analysis of the concurrent of hypopharyngeal esophageal cancer at the same time, we choose a selective screening test for every one having a symptoms of hypopharyngeal esophageal double primary cancer, We hope to have more clinical data and multicenter experiments to find the best treatment.

Conflict of interest: None is mentioned.

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