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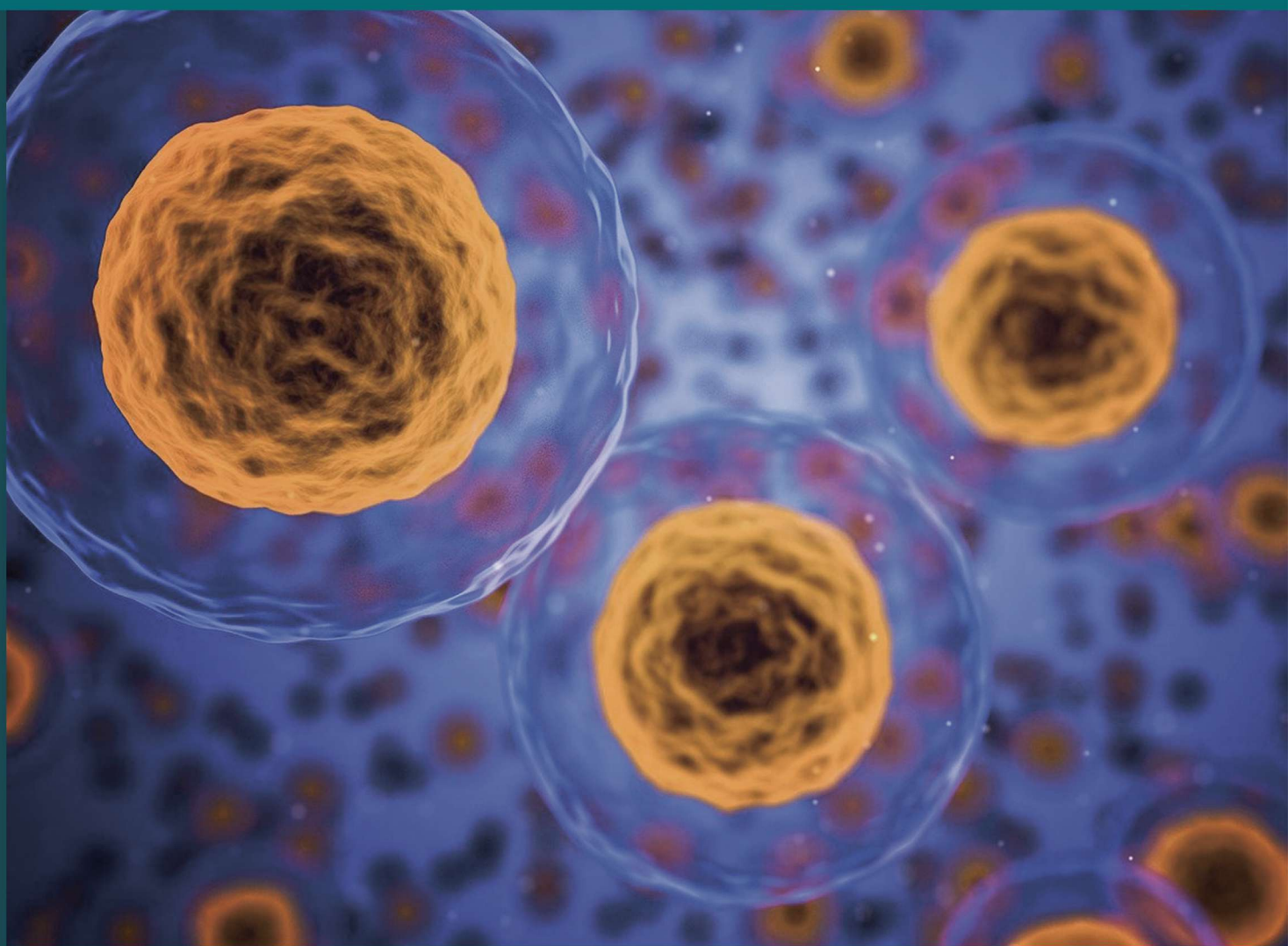

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REVIEW

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ARTICLE

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Pseudomyxoma Peritonei of Appendiceal Origin - 801 Cases from a Single Institution in China

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ABSTRACT

Aim: As more and more centers has published their treatment results of pseudomyxoma peritonei (PMP) with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), the data from China is missing. Myxoma Department of Aerospace Hospital is the biggest center treating PMP in China. The purpose of this study is to report the early and long-term outcomes for PMP from this single center. **Methods:** 801 appendix-derived PMP out of 1008 consecutive patients treated in Myxoma Department of Aerospace Hospital between 2008 and 2019 were retrospectively analyzed. **Results:** Complete cytoreductive surgery (CCRS) was achieved in 240 (30%) patients with median PCI of 14(1~39), and the rest had maximal tumor debulking (MTD), HIPEC was implemented in 96.3% of CCRS and 78.6% of MTD. The major morbidity (grade III/IV) was 11.4% and the 30-day operative mortality is 0.7%. The 5- and 10-year OS of CCRS was 76.9% and 64.1%, which is significantly higher than MTD (5-, 10-year OS as 36.1%, 27.1%; $p<0.001$). On the univariate analysis, all prognostic factors (gender, PSS, interval time, prior chemotherapy, prior HIPEC, Peritoneal Cancer Index (PCI), completeness of cytoreduction (CC), HIPEC, pathology, present of serous ascites) were found to be associated with overall survival except for age. On multivariate analysis, only PCI>20, MTD, high pathologic grade and without HIPEC were independent factors predicting poorer prognosis. **Conclusions:** CCRS +HIPEC can benefit PMP well with controllable risks. MTD+HIPEC may benefit PMP as well when CCRS cannot be achieved after fully asscessment by an experienced peritoneal maglignacy center, but the surgery should be performed as limited as possible.

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1. Introduction

PMP is an extremely rare clinical condition caused by the widespread implantation of mucinous tumor cells in the abdominal cavity through "redistribution phenomenon" described by professor Sugarbaker [1], and it usually had a relatively long and slow progressing natural course. These relatively inert cells mostly come from appendiceal mucinous neoplasms counting about 87.2%~94% according to previous studies [2-5]. Without appropriate treatment, the quality of life and prognosis can be really poor among these patients. In early report of 44 PMP patients treated by debulking surgery or combined with radiation therapy in Mayo Clinic, 35 died after tracing for 5 years [6]. And the later researches reported a 76% and 91% recurrence rate without the comprehensive treatment plan of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) [7,8], and mostly occurred in 2.5 years. As the latter combined panel gradually applied in clinical treatment, we had already got some achievements. The 10-year overall survival was as high as 54~70% when complete CRS(CCRS) can be achieved according to large sample size studies more recently, combined with HIPEC undoubtedly [9-12].

Though CRS+HIPEC has become the "gold standard" for PMP among almost all peritoneal malignany diagnosis and treatment centers, it still not widely recognized by other surgeons due to its relatively high mobility and mortality and lack of randomized controlled trails (RCT) [13-15]. Cause of the rarity of PMP and the long nature course, RCT may not be implemented and even for a very long time in the future. Thus, a lot high volume center had published their research results, but data from China is still missing.

The Myxoma Department of Aerospace Hospital is currently the largest PMP diagnosis and treatment center in China. More than 1000 PMPs have been treated in this center since 2008. Although there are still major limitations on knowledge of PMP in China and patients with early stage or local metastasis are rarely seen in our center, we still wish to share our treatment experience and summarize the current situation of PMP in China.

2. Method

2.1 Patients and Preoperative Management

A prospective database of all patients (N=1008) in our tertiary care center treated for PMP between Jan 2008 and Dec 2019 was retrospectively analyzed. Exclusion criteria are as follows: (1) without surgery as the first treatment strategy; (2) underwent palliative surgery simply to relieve clinical symptoms or accepted "open and close" surgery; (3) PMP originated from extra-appendix. The definition and pathological classification for PMP are based on the PSOGI experts' consensus in 2016 as follows [16]:

(1) Acellular mucin;

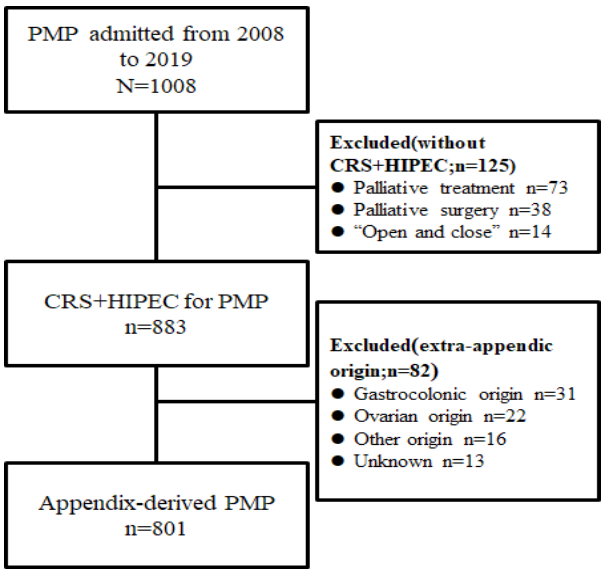
(2) Low-grade mucinous carcinoma peritonei (LGMCP);

(3) High-grade mucinous carcinoma peritonei (HGMCP);

(4) High-grade mucinous carcinoma peritonei with signet ring cells (HGMCP-S)

The films without accurate classification were re-read by pathologist.

Enhanced abdomino-pelvic CT with oral contrast angent, serum tumor marker tests (CA19-9, CA125, CEA), gastroscopy, colonoscopy, cardiopulmonary function evaluation were routinely implemented before surgery.



Flow-chat

2.2 Surgical Strategy

A midline incision was adopted for all PMP patients. At first, the abdominal cavity was fully explored and the extent of tumor burden was carefully calculated and using Peritoneal Cancer Index (PCI) [17]. Peritonectomy combined with visceral resections intending to remove all the macroscopic tumors as much as possible was processed as Sugarbaker previously described [18,19], taking into account its expected morbidity/mortality. The completeness of cytoreduction (CC) is as follows: CC-0: no visible residue; residual tumor: CC-1: <2.5mm; CC-2: 2.5mm~2.5cm; CC-3: > 2.5cm when CC-0/1 is defined as complete cytoreductive surgery (CCRS) and

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CC-2/3 as maximal tumor debulking surgery (MTD) with unresectable focus [20].

MTD in our department took place in the following 2 situations:

(1) the small bowel is widely involved with the remaining less than 1.5 metres or mesenteric involving caused retraction;

(2) tumors invade the serosa of stomach circumference or hepatic pedicle.

In the follow-up period for these patients with MTD, only if severe clinical symptoms which may seriously affected quality of life occurred (such as obstruction, fistula et.al), another operation was chosen cautiously.

2.3 Hyperthermic Intraperitoneal Chemotherapy

HIPEC was performed after CRS and before digestive tract reconstruction with a closed procedure. The circulation speed was controlled at 800~1000ml/min, inlet temperature was controlled at 43.5°C when the outlet was above 41°C during the therapy for 60min. MMC 30mg/cisplatin 60~80mg was used with a solvent of physiological saline.

3. Data Collection and Analysis

All patients were followed up every 3 to 6 months in the first 5 years after surgery with enhanced abdomino-pelvic CT and tumor marker evaluation (CEA/CA125/CA19-9) in our center, and then annually after 5 years. The outset of follow-up was the date of surgery in our hospital, and the overall survival (OS) was counted. The follow-up period was until Feb, 2019. Perioperative data and follow-up results were collected statistically after. Post-operative complications were graded by Clavien-Dindo criteria, with grade III-IV as the major complication and grade V as the perioperative death (30-day) [21].

Statistical analysis was performed using SPSS 25.0. The *t*-test was used for the measurement data and Rank sum test (Mann-Whitney *U* test) for those which do not meet the normal distribution. The x^2- test was used for the count data. The overall survival was compared using Kaplan-Meier method by log-rank test. The prognostic univariate and multivariate analysis were performed using the *cox* proportional hazard model. P <0.05 was defined as significant.

4. Results

4.1 Clinicopathologic Features

From Jan 2008 to Dec 2019, 1008 patients diagnosed as PMP were treated in the Myxoma Department of Aerospace Hospital. And 801 of them who received the comprehensive plan of CRS and HIPEC and pathologically confirmed as appendix origin were included in this study. 627(78.3%) had received more than one surgical procedure before with a median interval time of 16 months. 172(21.5%) had previously received HIPEC and 246(30.7%) received system chemotherapy without CRS. The patient characteristics are shown in Table 1.

Table 1. characteristics of patient underwent CRS+HIPEC with appendix-derived PMP

Variable		n(N=801)	%
gender	male	322	40.20%
	female	479	59.80%
age	mean(range)	58(17~82)	
PSS	0	174	21.70%
	1	219	27.30%
	2	118	14.70%
	3	290	36.20%
interval time[a]	≤12m	336	41.90%
	>12m	465	58.10%
Prior chemotherpy	without	555	69.30%
	with	246	30.70%
Prior HIPEC[b]	without	629	78.50%
	with	172	21.50%
CEA(ng/ml)	median(quartile range)	31(6.7~94.2)	
CA125(U/ml)	median(quartile range)	46.5(22.1~93.9)	
CA19-9(U/ml)	median(quartile range)	45(10~249)	
PCI	median(range)	28(1~39)	
PCI	0-9	106	13.20%
	10-19	72	9%
	20-29	284	35.50%
	30-39	339	42.30%
CC	CC-0	101	12.60%
	CC-1	139	17.40%
	CC-2	237	29.60%
	CC-3	324	40.40%
HIPEC	without	129	16.10%
	with	672	83.90%
pathology	acellular	20	2.50%
	LGMCP	504	62.90%
	HGMCP	181	22.60%
	HGMCP-S	54	6.70%
	unknown	42	5.20%
ascites	mucious	274	34.20%
	serous	253	31.60%
	mixed	87	10.90%
	without	187	23.30%

Notes:
[a], the time from diagnosis of PMP to CRS+HIPEC in our department; [b], previously received HIPEC without CRS.

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CCRS was achieved in 240 (30%) patients dispite a median PCI of 14(1~39), of which 30.8% (74/240) were 20-29 and 5.4% (13/240) were above 30. CC-2 and CC-3 happened in 237(29.6%) and 324 (40.4%) patients each with the median PCI of 27 and 32($p<0.001$). HIPEC was implemented in 96.3% of CCRS and 78.6% of MTD. Except for 42 patients remained unclear pathological grade, low-grade PMP is the most common pathological type accounting for 66.4% (504/759). CCRS was achieved in 27.6% (65/235) and 32.8% (172/352) of patients in the HGMCP+/-S group and acellular/LGMCP group, respectively, with no significant difference between the two groups.

Ascites can be detected in 76.7% and mostly mucious or mixed, but serous ascites existed in 31.6%. And we found serous ascites associated with the grade of tumors (acellular/LGMCP vs HGMCP+/-S: 37.8% vs 55.3%, $p<0.001$). Also, the high-grade+/-S were with significantly higher tumor marker levels (median; CEA: 36.4 ng/ml vs 28.7ng/ml, $p=0.008$; CA125: 66.5U/ml vs 38.5 U/ml, $p<0.001$;CA19-9: 90.7U/ml vs 36.8U/ml, $p<0.001$). Overall, the mean operation time was 476 min (105~859) and the median blood loss is 1500ml (20~11000).

4.2 Morbidity and Mortality

The major morbidity (grade III/IV) was 11.4% (91/801) in the entire cohort. Intestinal fistula and anastomotic leakage were the most common counting for 44% (40/91), followed by post-operative pleural effusion (24.2%;22/91) and intra-abdominal bleeding (7.7%;7/91). Six patients died within 30 days after surgery, 3 died of abdominal infection, 2 died of respiratory failure, and 1 died of renal failure. The 30-day operative mortality is 0.7%. Comparing CCRS with MTD, the overall severe perioperative complications were slightly higher in MTD group (15.7% vs 9.6%, $p=0.059$).

4.3 Survival Outcomes

Excluding 63(7.9%) patients with inadequate follow-up information from the survival analysis, the median follow-up for the rest is 39 months (1-143). The 3-, 5-and 10-year overall-survival (OS) was 62.7%, 47%and 37.9% for the whole patient population. The 5- and 10-year OS was 76.9% and 64.1% when CCRS occurred, which is significantly higher than MTD (5-, 10-year OS as 36.1%, 27.1%; $p<0.001$). And CC-0 has a much better prognosis than CC-1($p<0.01$) (Figure 1). The benefit seemed also to be found in CC-2 than CC-3(5-year OS 37% vs 30%, $p=0.034$), but the significant difference disappeared when adjusted by tumor grade, HIPEC and PCI ($p=0.506$; HR=0.900, 95%CI: 0.659-1.228).

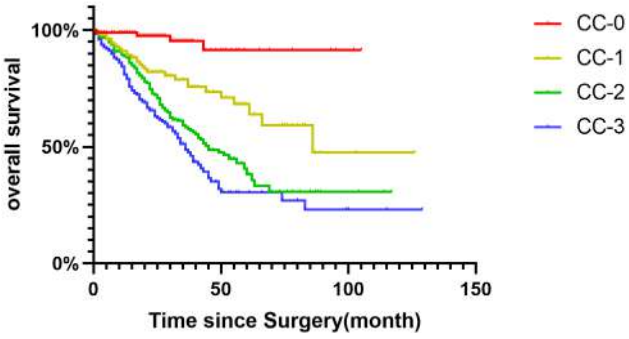

Figure 1. Overall survival by completeness of cytoreduction(CC)

The median OS of MTD combined with or without HIPEC was 44 months and 24 months ($p<0.001$). The survival advantage of HIPEC is more pronounced in MTD without serous ascites ($p<0.001$) (Figure 2) compared with the opposite ($p=0.118$) (Figure 3).

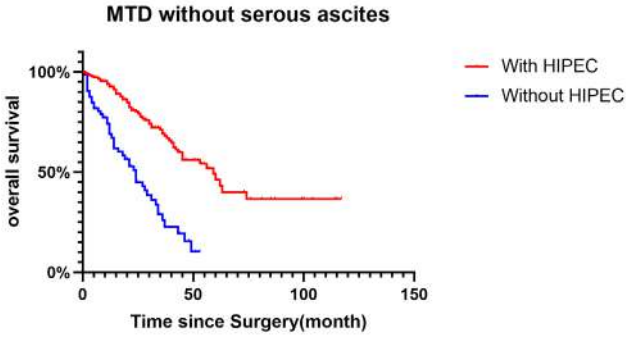

Figure 2. Overall survival by HIPEC for MTD without serous ascites

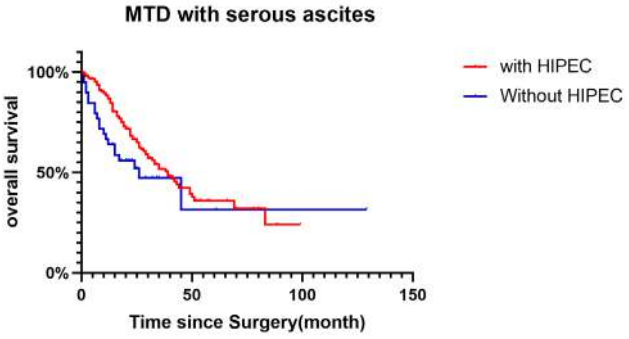

Figure 3. Overall survival by HIPEC for MTD with serous ascites

No deaths occurred among the patients diagnosed with acellular mucin and significant survival difference can be found between each grade (Figure 4). The worst prognosis was associated with HGMCP-S with a median OS of 21

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months. The median OS for LGMCP and HGMCP was 83 months and 39 months (p<0.001).

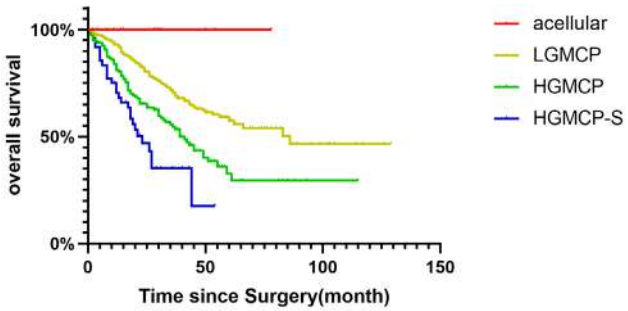

Figure 4. Overall survival by different pathological grades

On the univariate analysis, all prognostic factors were found to be associated with OS except for age, as outlined in Table 2. On multivariate analysis, PCI≤20, CCRS, acellular/LGMCP and HIPEC were independent factors predicting a better prognosis (Figure 5).

Table 2. Univariable and multivariable analysis for overall survival after CRS+HIPEC

		Univariable OS		Mutivariable OS	
		HR(95%CI)	p	HR(95%CI)	p
Gender	female	0.754 (0.588-0.966)	0.025	0.750 (0.553-1.018)	0.065
Age		1.007 (0.996-1.019	0.227		
PSS	0/1	0.712 (0.555-0.914)	0.008	0.911 (0.651-1.274)	0.586
Interval time	≤12m	0.69 (0.532-0.895)	0.005	1.101 (0.797-1.52)	0.561
Prior chemotherpy	without	0.541 (0.421-0.694)	<0.001	0.783 (0.583-1.051)	0.104
Prior HIPEC	without	0.66 (0.493-0.882)	0.005	0.913 (0.65-1.282)	0.6
PCI	≤20	0.283 (0.188-0.425)	<0.001	0.48 (0.295-0.781)	0.003
CC	0-1	0.291 (0.202-0.418)	<0.001	0.607 (0.395-0.933)	0.023
HIPEC	with	0.348 (0.264-0.459)	<0.001	0.473 (0.373-0.659)	<0.001
pathology	Low-grade	0.456 (0.351-0.593)	<0.001	0.493 (0.373-0.65)	<0.001
Serous ascites	without	0.594 (0.463-0.761)	<0.001	0.79 (0.597-1.044)	0.098

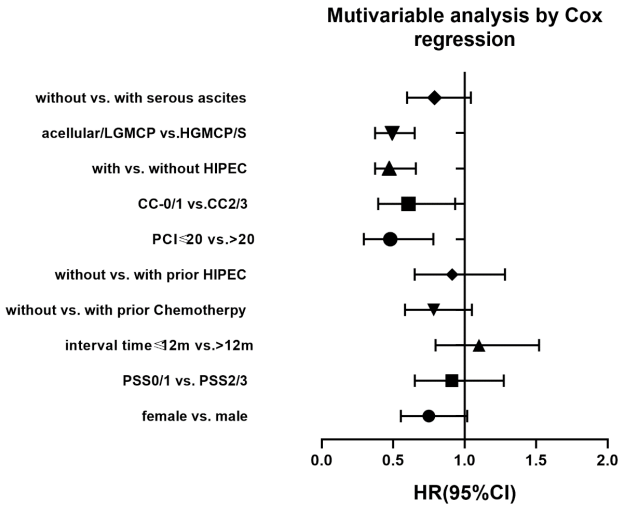

Figure 5. Forest plots of cox regression

5. Discussion

AS Sugarbaker proposed the peritonectomy technique and the comprehensive treatment model of CRS + HIPEC in the 1990s, more and more centers have reported the good survival outcomes and prognostic factors of CCRS + HIPEC for PMP, but few centers had treated more than 500 cases [2,9-12,14,15,22]. Prior to this study, professional team of Li Yan from Shijitan hospital has already pubilished their results which evaluated the safety of CRS + HIPEC in PMP and summarized its clinicopathological features [23,24], but still the data from China is lacking. Department of Myxoma of the Space Center Hospital is currently the largest PMP treatment center in China. This article aimed to summarize and share the experience of this single center with a large volume.

The 5-year and 10-year survival rates of patients who achieved CCRS and MTD in this study were 76.9%, 64.1%, and 36.1%, 27.1%, the overall major morbidity was 11.4%, and the 30-day perioperative mortality was 0.7 %, Which is similar to previous researches [10-12]. CC or HIPEC may be not presented as independent factors in several centers [11,12], but the long-term prognosis of all CCRSs were excellent and there is no doubt that in selected patients to achieve CCRS as much as possible to improve the long-term survival with the controllable risks.

However, based on the current situation in China, a vast majority of patients have a huge tumor burden in the abdominal cavity at the time of consultation, and the stomach and small intestine are seriously involved and lost the possibility of CCRS. Previous study has reported CRS+HIPEC in 100 patients which with PCI≥28 and the radical resection rate was 54% [25]. In another research, the rate of CCRS even in HGMCP with a median PCI

of 32 can reach 84% [26]. It is undeniable that we have a large gap with them. At present, we still have major limitations when dealing with tumors involved in hepatic pedicle. However, few studies have focused on this part of patients with MTD. Considering the relatively higher risk than traditional treatment, whether MTD + HIPEC should be performed is still ongoing debate [15,27]. Although some researchers believe that MTD can still benefit PMP in longer OS and improved quality of life, it cannot be proved without suitable controls [28,29]. In this study, the proportion of MTD is huge. Although the residual tumors of CC-2 are significantly smaller and lower tumor burden post-operation, we failed to prove CC-2's significant survival advantage over CC-3, consistent with the earlier data reported by Sugarbaker [30]. For patients who cannot reach CCRS, it seems that expanding the scope of surgical resection does not obtain any survival benefit. Theoretically, the penetration depth of HIPEC cannot cover the residual tumors after MTD and HIPEC was not recommended by previous studies. Of the 174 MTDs reported by Glehen et al., the 5-year OS of patients who did not receive HIPEC treatment is only 10%, compared to 32%. On multivariate analysis HIPEC was an independent factor for OS in MTD in their study [31]. Although some studies suggest that the presence of serous ascites should be considered for HIPEC [11], the results of this study showed that MTD combined with HIPEC can still achieve longer survival when PMP without serous ascites. More importantly, the Patients with serous ascites do not seem to benefit from HIPEC ($p = 0.118$).

HGMCP+/-S were usually associated with serous ascites (55.3%) and significantly higher tumor marker levels (CEA, CA125, CA19-9), while acellular / LGMCP were usually mucinous. That can be used in preoperative and intraoperative judgment. Although there was no significant difference in the proportion of CCRS in different pathological grades, the prognosis of HGMCP+/-S, especially HGMCP-S was much worse than acellular / LGMCP. The median survival of HGMCP-S after CRS + HIPEC in this study was only 21 months. C. Mumzo-Zuluaga [26] reported 65 cases of HGMCP-S with the median survival of 2.2 years, though 83% of the cases reached CCRS. HGMCP+/-S were independent predictor of poorer survival here had been proved previously [11,12,28,32].

PCI is also one of the independent risk factors affecting OS, as H. Anderasson and O. Glehen reported [15,33]. The worse prognosis of high PCI is considered to be associated with lower CCRS probability. Based on the result of a multi-center study with the currently largest sample size, even in patients with PCI> 30, 10-year OS can still reach 68% if achieved CCRS [10]. Therefore, for patients with high tumor burden, if there is a possibility of complete resection after assessment by an experienced center, CRS + HIPEC should be implanted for the optimal prognosis.

Overall, CCRS +HIPEC should always be the primary goal for PMPs regardless of PCI and pathology. Once CCRS cannot be achieved after fully evaluation in the experienced peritoneal maglignacy center, MTD+HIPEC should be performed but as limited as possible to minimize the surgical trauma.

Of course, this study has major limitations. First of all, as the average rate of CCRS reported by S.Kusamura was 84.4% [34], obviously we still have a very long way to go. Most of the appendixes were previously removed but without clear pathological classification, the pathological grades of appendiceal mucinous neoplasm were unknown. Also, as a retrospective study, partial data loss (such as lymph node metastasis status, recurrence data *et al*.) and case selection bias might be factors affecting the results. Whether PMP with limited metastasis just around appendix can benefit more or not from CCRS+HIPEC cannot be proved in this study.

Surgery techniques and the understanding of PMP have been constantly improving worldwide as time goes, but still a lot of things remained unclear. We have treated PMP with increasing numbers and the annual volume nearly 200 in recent years. This article filled the blanks of China and we are looking forward for the development in future.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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ARTICLE

Research Progress of the Treatment of PD-1 Immune CheckpointInhibitors in Oral Squamous Cell Carcinoma

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ABSTRACT

Targeted immune checkpoint-based immunotherapy has achieved remarkable success in the treatment of malignant tumors. Immune checkpoint inhibitor-programmed cell death protein 1 (PD-1) antibody opens a new era of immunotherapy for platinum-refractory recurrent/metastatic oral squamous cell carcinoma (OSCC). The overall survival of patients treated with immunological checkpoint inhibitors was significantly prolonged, and the overall incidence of grade 3-4 drug-related adverse events (AEs) occurred was lower; however, there are still some challenges to the PD-1's application in OSCC clinic treatment. This article is just to briefly highlight the development of such application to date.

1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is the 6th most common malignant tumor category worldwide. Oral carcinoma, the most common subcategory of HNSCC, can be the 9th - if alone - on the same ranking list. Each year, more than 300,000 people are affected by oral carcinoma, in which OSCC accounts for 90%. At present, the treatment of OSCC mainly consists of traditional surgery, radiotherapy and chemotherapy. More than 50% of OSCC patients have tumor recurrence or metastasis within 3 years; and more than 145,000 patients die from oral malignant tumors each

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year. The recorded 5-year survival rate is about 50% [1-4].

In recent years, with the development of research on the relationship between immunity and tumor, immunotherapy has become an important means of tumor therapy further to traditional surgery, radiotherapy and chemotherapy. In 2018, Prof. Allison and Prof. Honio won the Nobel Prize in Physiology or Medicine for their research work on cytotoxic T lymphoid-associated antigen-4 (CTLA-4) and PD-1 in the immune checkpoint. Since 2010, the immunosuppressive checkpoint molecules have been recognized as new targets for immunotherapy, whose curative effectiveness was initially demonstrated in treatment of advanced melanoma and then gradually applied to different types of malignancies with varying degrees of benefit. In the second half of 2016, two PD-1 immune checkpoint inhibitors, Nivolumab (Opdivo) and Pembrolizumab (Keytruda), were approved by the FDA for treating relapsed and refractory HNSCC. This means currently there are two PD-1 immune checkpoint inhibitors approved for treating OSCC. According to the current research progress, compared with the traditional treatment, PD-1 immunocheckpoint inhibitor has better prospect on treatment of advanced OSCC.

2. Immune Checkpoint Protein

As the core executor in the process of anti-tumor immunity, T cells have two types of stimulation signal molecules on their surface, namely, co-stimulation molecules and co-inhibition molecules. The process which T cells exert an immune response involves being activated first by antigen recognition signal, and then fine-regulating T cell response by co-stimulating signal molecules. The co-inhibition molecules that play a negative immune regulatory role are also called immune checkpoint molecules. Common checkpoint proteins in tumor immunotherapy include PD-1, CTLA-4, T cell immunoglobulin and Mucin Domain 3(TIM-3), LAG 3, T cell immunoglobulin and ITIM domain (TIGIT), etc. Among which the PD-1 and CTLA-4 are most focused due to apparent effectiveness of their functions in treatment of malignant tumors.

3. Biological Characteristics of PD-1 and Its Ligand

A member of the CD28 superfamily, PD-1, was originally cloned from apoptotic small T cell hybridoma 2B4.11 and is the immunoglobulin superfamily Type I transmembrane glycoprotein. It is mainly expressed on the surface of activated T lymphocytes, NK cells, monocytes and B lymphocytes. As an important immune checkpoint for immunosuppression of tumor-infiltrating T cells, PD-1 is up-regulated in a variety of tumor microenvironments, such as gastric cancer, ovarian cancer, pancreatic cancer, hematologic tumors, etc. PD-1 exists as monomer on the cell surface and is composed of an extracellular IgV region, a transmembrane domain, and an intracellular tail [5]. There are four N-ligand glycosylation sites in the extracellular immunoglobulin - like domain for binding to ligands. There are two tyrosine residues in the intracellular area: the terminal N is the immunoreceptor tyrosine-based inhibitory motif (ITIM), and the terminal C is immunoreceptor tyrosine switch motif (ITSM).

PD-1 receptor has two ligands: PD-L1 (CD274/ B7-H1) and PD-L2 (CD273/B7-DC). PD-L1 has a wider expression spectrum than PD-L2, and is mainly expressed in hematopoietic and non-hematopoietic cells (including epithelial cells, vascular epithelial cells, stromal cells, etc.). Under the action of inflammatory factors (including type I and type II interferon, TNF-α and VEGF) or tumor cells, PD-L1 is induced to be expressed in stromal cells and tumor cell surfaces of tumor tissues. PD-L1 is highly expressed in many solid tumors, such as non-small cell lung cancer, melanoma, prostate cancer, breast cancer, renal cell carcinoma, etc [6-7], also in HNSCC.

Current studies have shown that PD-1 binding with ligands blocks the activation of T cells and thus blocks their proliferation through the following pathways, to make the T cell immune response incompetent: First, in the case of simultaneous mating with T cell receptor (TCR), the phosphatase SHP-2 with the SH2 domain is recruited by the intracellular ITSM to block the phosphorylation mediated by the activation of TCR molecules. This prevents T cell activation and cytokine production. Secondly, the combination of PD-1 and PD-L1 can inhibit the activation of CD28-mediated phosphoinositide-3-kinase (PI3K), dephosphorylate the phosphatidylinositol 3-kinase B -protein kinase B (PI3K-AKT), and thus inhibit T cell activation. This inhibitory effect of PD-1 can be reversed by enhanced CD28 or signal transduction and activator of transcription (STAT) cytokines.

Based on the mechanism described above, PD-1 inhibitors, and PD-1 ligand PD-L1 inhibitors, block the interaction between PD-1 and PD-L1, thereby blocking the immune escape of tumors. Blocking the PD-1/PD-L1 signaling pathway has achieved a relatively long-lasting anti-cancer response. With breakthrough progress of efficacy on the treatment of various malignant tumors such as melanoma, non-small cell lung cancer, Hodgkin's lymphoma, genitourinary system tumors, colorectal cancer, etc., PD-1 inhibitors continues to expand its tumor

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treatment spectrum [8].

PD-L2 and PD-L1 share 37.4% homology at the gene level. PD-L2 mainly involves in regulating the immune response caused by natural environmental antigens. The expression and regulation mechanisms of PD-L1 and PD-L2 are different. Previous studies have shown that PD-L2 is mainly expressed in dendritic cells, monocytes, mast cells derived from bone marrow, and B cells in the germinal center. Also, it's slightly expressed in vascular endothelium and T cells. Recent studies have used innovative immunohistochemical methods to analyze more than 400 tissue samples involving 7 different types of tumors, including renal cell carcinoma, bladder cancer, melanoma, non-small cell lung cancer, triple negative breast cancer, gastric cancer, and HNSCC. The results showed that there was no PD-L2 expression in the tumor cells of renal cell carcinoma tissue samples; very few tumor cells expressed PD-L2 in melanoma samples; the expression level of PD-L2 was significantly increased in gastric cancer and triple-negative breast cancer; and more than half of tumor cells overexpress PD-L2 in HSNCC tissue samples [9].

4. PD-1 and Its Ligand: Their Expression in OSCC and Anti-Tumor Efficacy

As the main ligand of PD-1, PD-L1 is not only overexpressed on the surface of t, umor cells in OSCC, but also expressed on the surface of immune cells in the tumor microenvironment, including regulatory T cells (Tregs), natural killer (NK) cells and Antigen presenting cells (APCs) [10-12]. Previous studies showed that the expression of PD-1 and PD-L1 on the surface of CD4+ and CD8+ T cells in the peripheral blood of OSCC patients was significantly higher than that of the control group; also, the study found that the level of soluble PD-1 in the plasma of OSCC patients was also significantly higher than the control group [13]. In addition, the expression of PD-1 in the peripheral blood of patients with OSCC or with precancerous lesions of actinic cheilitis (AC), is higher than that of normal people, while the expression of PD-1 on CD4+ and CD8+ T cells in the tumor site of OSCC patients was higher than that of the AC ones [14]. Another study showed that compared with normal oral mucosa, the expression of PD-L1 in OSCC is significantly up-regulated, and such expression of PD-L1 in peripheral blood of patients with lymph node metastasis is significantly higher than that of patients without lymph node metastasis. Research suggests that in addition to the local area of the tumor, the expression of immune checkpoints in the entire system should also be considered [15].

The correlation between the expression or threshold of PD-1 ligand and the anti-tumor immune efficacy of PD-1 immune checkpoint inhibitors remains unclear. Reviewing the approved clinical trials of PD-1/PD-L1 drugs, the current expression of PD-L1 is basically an item for mandatory check. Known results suggest that to most cancers approved to be treated with immune checkpoint inhibitors, such as non-small cell lung cancer, melanoma, urothelial carcinoma, OSCC (HNSCC), etc., PD-L1 expression is positively correlated with the objective response rate and/or survival time [16]. It is currently believed that the expression of PD-L1 in tumor cells exceeding 10% is related to a poor prognosis, and it is generally regarded as a demarcation point related to clinical efficacy. Related studies showed that the PD-L1 expression rate of OSCC samples is 10% to 15%, which is negatively correlated with tobacco and alcohol consumption, and PD-L1 expression is correlated with tumor recurrence and survival rate [17]. However, there are still some defects of PD-L1 expression in clinical applications: (1) The expression of PD-L1 in some tumors (such as renal cell carcinoma) has no correlation with clinical benefit; (2) Even in the same type of tumor, the relationship between the expression of PD-L1 and the efficacy may be contrary to the prediction [18].

There are few studies on the correlation between PD-L2 and PD-1 immune checkpoint inhibitors in anti-tumor efficacy. Current researches suggest that PD-L2 is overexpressed on the surface of OSCC tumor cells. Jennifer Yearley's study showed that among 172 patients with relapsed or metastatic HNSCC treated with pembrolizumab, the ORR of patients with PD-L1 and PD-L2 expression both positive was 27.5%, while the ORR of patients with positive PD-L1 expression and negative PD-L2 expression was only 11.4%.Therefore, the expression level of PD-L2 can be used as supplementary information, together with the expression level of PD-L1, as predictors of tumor efficacy [5]. This emphasizes the importance of PD-L2 expression, which is conducive to a better understanding of the tumor biological significance of PD-1 signaling pathway.

5. Application of PD-1/PD-L1 Checkpoint Inhibitors in OSCC Treatment

Since the second half of 2016, nivolumab and pembrolizumab have been approved by FDA for the treatment of oral cancer. Pembrolizumab, also known as MK-3475, is the first PD-1 monoclonal antibody approved for clinical trials of recurrent/metastatic HNSCC. Among the 132 patients in the experimental group of the multicenter phase I

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clinical trial (KEYNOTE-012), 49.3% of them obtained partial response or stable disease, of which 78% were PD-L1 positive patients, the response rate of PD-L1 positive patients was 20%, and 86% of patients showed a durable response. The patients who received a response after treatment in this study included HPV+ patients as well as HPV- patients. Research showed a low incidence of adverse drug reactions, with only 7.6% of patients with> grade 3 drug-related adverse reactions [19].

Pembrolizumab has shown anti-tumor activity and controllable drug toxicity in early trials. The phase III clinical study KEYNOTE-040 further observes its efficacy and safety. From December 24, 2014 to May 13, 2016, 247 patients were randomly assigned to the pembrolizumab group, and other 248 patients were randomly assigned to the standard chemotherapy group. As of May 15, 2017, 181 (73%) patients in the pembrolizumab group and 207 (83%) patients in the standard treatment group had died. The median overall survival of the pembrolizumab group and standard treatment group was 8.4 months vs. 6.9 months respectively; and the overall incidence of> grade 3 drug-related adverse reactions in the pembrolizumab group was lower (33 cases [13%] vs 85 cases [36%]). The most common treatment-related adverse events of pembrolizumab were hypothyroidism (33 cases [13%] patients) and fatigue (43 cases [18%]) [20]. Another phase III clinical study (KEYNOTE-048) was made based on platinum-resistant HNSCC patients with relapse and metastasis, its intermediate study results were announced in 2018 by the European Society of Medical Oncology (ESMO): Compared with the standard chemotherapy regimen EXTREME (PFE: carboplatin/cisplatin, 5-FU, cetuximab + cetuximab maintenance), among the 882 patients who used pembrolizumab as the first-line treatment, the combined positive score of PD-L1 expression (CPS. The number of PD-L1 positive cells in tumor cells, lymphocytes, and macrophages) was ≥20 with an OS rate of 39%, while OS was only 22% in the group of patients CPS ≥1.

In the multicenter phase III clinical study (CHECKMATE-141) of Nivolumab for the treatment of platinum-resistant recurrent or metastatic HNSCC, the overall survival of patients receiving nivolumab (240 cases) and docetaxel treatment were 7.5 vs 5.1 months respectively. The 1-year overall survival rate was 36.0% vs 16.6%, and the study showed that in nivolumab treatment, the overall incidence of drug-related adverse reactions of >3 grade was lower (13.3% vs 35.1%) [22]. Based on the above research data, in November 2016, the FDA approved nivolumab for the treatment of patients with recurrent or metastatic HNSCC [22].To observe the long-term efficacy and safety of the drug on PD-L1-expressing patients, a preliminary analysis with 2-year follow-up was made and it showed that Nivolumab can significantly improve OS and maintain controllable and consistent safety. But at the same time studies also showed that OS has no correlation with PD-L1 expression and HPV infection status. However, in the treatment of Pembrolizumab, the results of KEYNOTE-040 and KEYNOTE-048 support that PD-L1+ can significantly improve the survival time of patients.

In the phase I clinical trial of HNSCC, PD-L1 antibody also showed a certain degree of clinical efficacy. Currently, representative antibodies targeting PD-L1 include durvalumab (MEDI-4736), atezolizumab (MPDL3280A) and BMS-936559 (MDX1105), which have been used as monotherapy or in combination with other drugs in clinical trials of multiple tumors [23]. The durvalumab (IgG1 isotype) study recruited 62 patients with R/M HNSCC. The results of the study showed an ORR of 12%, and a sustained response time of 4 to 43 weeks was obtained. The response rate of PD-L1 positive patients was 25%. The 24-week disease control rate of all patients was 16%, which was 25% of PD-L1 positive patients [24]. In addition, there are randomized phase I/II clinical trials evaluating durvalumab combined with AZD9150 or AZD5069 (NCT02499328) for patients with metastatic HNSCC. The study is currently evaluating clinical safety, efficacy and ORR [26]. There are few studies on Atezolizumab in the treatment of HNSCC. According to the clinical deadline of April 30, 2013, a study included a total of 277 patients with advanced cancer, with a response rate (RR) about 17%, but the number of HNSCC was small (n = 6) [26]. Currently in clinical trials of HNSCC, PD-L1 antibody is combined with other immune checkpoint inhibitors to improve efficacy. Some trials evaluating the combination of durvalumab monotherapy and tremelimumab (anti-CTLA-4) are ongoing (NCT02551159, NCT02369874, NCT02319044), and the clinical results of such immunotherapy combinations are highly anticipated [27,28].

6. Problems and Challenges of PD-1 Immune Checkpoint Inhibitors in OSCC Treatment

PD-1 immune checkpoint inhibitors currently have achieved good clinical effects in the treatment of HNSCC and other malignant tumors, but only a small number of patients can benefit from monotherapy. Therefore, in order to improve the disease response rate and long-term efficacy, some preclinical studies and clinical trials have used PD-1 combined with radiotherapy, radiotherapy, targeted drugs and other immune checkpoint inhibitors for

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the treatment of HNSCC, and achieved varying degrees of clinical efficacy initially. Such as Pembrolizumab combined with cetuximab in the treatment of HNSCC (NCT02586207) [29]. Pembrolizumab combined with platinum drugs or radiotherapy is used for neoadjuvant treatment of HNSCC surgery, exploring the use of pembrolizumab for resectable HPV-negative, and neoadjuvant and/or postoperative adjuvant treatment of patients with stage III/IV HNSCC [30-31].

Although a number of trials have confirmed the effectiveness and the short-term safety of anti-PD-1/PD-L1 pathway in the treatment of tumors, preliminary clinical research data showed that patients with different types of malignant tumors, including OSCC patients, have primary resistance to PD-1/PD-L1 drugs as high as 60%, therefore, it is urgent to further improve the treatment response rate and long-term efficacy [32]. Since the PD-1/PD-L pathway plays an important role in autoimmune regulation and tumor immunity, with the complexity of the tumor microenvironment, the primary drug resistance mechanism of PD-1 antibodies is also complicated. The current research on the resistance mechanism of PD-1 antibodies mainly proposes the following points: weak tumor cell immunogenicity, limited immune cell infiltration within the tumor, tumor burden factors, different mismatch repair(dMMR) in solid tumors, and multiple expressions in the tumor microenvironment(TME) inhibitory receptors and pathways of immunosuppression induced by TME, etc. [33-35].

In response to the problem of resistance to PD-1 immune checkpoint inhibitors in the treatment of OSCC, besides improving the efficacy through combination with other treatments, researchers are also actively exploring resistance mechanisms and other solutions. Finding biomarkers for predicting efficacy is an effective way to achieve precision treatment of OSCC. Most current studies believe that PD-1/PD-L1 inhibitors have higher benefits for patients with PD-L1 positive tumors. Based on the current research results, it is still uncertain whether the effective rate of PD-1 inhibitors in the treatment of OSCC will be affected by the expression level of tumor PD-L1. Based on the current studies, there is currently no evidence that HPV infection is directly related to the effective rate of PD-1 inhibitors and the durable response rate of patient [36]. The expression level of PD-L2 can be used as supplementary information, combined with the expression of PD-L1 to be a predictor of efficacy.

In addition, the composition of the digestive tract microbial population is related to immune disorders and the occurrence and development of many malignant tumors. Two retrospective clinical studies emphasized that the application of antibiotics will affect the efficacy of immunotherapy, and proposed that to the patients with advanced tumors suppress immune checkpoints, their drug resistance (especially the PD-1/PD-L1 antibody) can be caused by the abnormal composition of intestinal microbes [37-38]. OSCC originates from the oral mucosal epithelium, and the oral microbiota is often exposed to external environmental factors. Compared with healthy controls, OSCC patients have a different microbiota composition in saliva, and the presence of specific bacteria is associated with the risk of OSCC. Current studies also found that the composition of the microbial population is related to the expression of HPV. The correlation between the composition of oral microbes and the resistance of immune checkpoint inhibitors needs to be further confirmed [39].

Immune checkpoint inhibitors have opened a new era of tumor immunotherapy, and PD-1 inhibitors have an important role in promoting the efficacy of OSCC treatment. However, the drug currently also faces a series of problems in clinical application, including clinical efficacy and immunotherapy-related side effects. To solve these problems, the researchers still have a long way to go.

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REVIEW

Busting Myths about SARS-CoV-2 Viral Pandemic to Non-medical Personnel

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ABSTRACT

Background: During these moments of anxiety, fear and to some extent despair, it is imperative for everyone to have access to the right information. This can be achieved through breaking down the science and medical terminologies used to express the scenarios emanating from the COVID-19 pandemic. **Forward:** This commentary focuses on the most asked questions that, when not answered with scientific grounds to convince the non-medics can result in non-science based "infodemics". The brief history behind COVID-19 pandemic, the science of SARS-CoV-2, the taxonomies used, a brief on the Pathophysiology of SARS-CoV-2, the genetic make up, most vulnerable indivduals, antibodies against COVID-19, mother to baby transmission, conspiracy theories reagading the virus being weaponized, mutations occurring with SARS-CoV-2 and reoccurrence of COVID-19 in the future are all explained at great length. The review made references to the existing publications regarding this pandemic. **Conclusion:** While the science regarding this virus is not exhausted, we confirmed that, the knowledge gap between non-medics and medics is wide. The results emerging from the pandemic to form data are questionable, so it is our collective responsibility to fight against this virus in order to stop further spreading by providing the right information to the public. If we would not come together to fight and win this battle, we might be witnessing many large cities turning into emerging epicenters of COVID-19.

1. Introduction

January 9th, 2020, the Chinese Center for Disease Control and Prevention (CDC) formally confirmed to the Wall Street Journal that, a novel coronavirus (CoVs) previously unknown to science has been reported to be responsible for an outbreak of respiratory illnesses. This emerging public health concern at the time will later be responsible for the first coronavirus pandemic[1,2]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19) is responsible for the current pandemic, which is affecting lives in various ways. The virus was first isolated in patients seen in Hubei province, Wuhan, China who were

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found to have pneumonia. The cluster of pneumonia cases were seen in patients who were suspected to have links to a seafood market. This lead to the closure and decontamination by the Chinese officials[3]. The World Health Organization (WHO) officially declared COVID-19 epidemic as a public health emergency of international concern (PHEIC) on Janury 30th and passengers with travel links to Wuhan are being subjected to screening[4]. A group of Chinese scientists on the 7th of January 2020, rapidly isolated the SARS-CoV-2 a β-coronavirus from a patient within a short time frame and subsequently genome sequencing was done for the global scientific community to join the science behind the new enemy of humanity[5].

This devastating pandemic has called for an urgent and highly professional containment measures to limit physical, mental and socio-economic problems. The expertise ranges from emergency response which includes, case detection, quarantine and isolation to the need for a more extensive evaluation of diagnostic capacities and preparedness, in anticipation of any disease epidemic[6,7]. Despite the previous outbreaks and the fatal outcomes associated with, evidence gathered from the media has it that, people around the world are seemingly not taking this pandemic gravely. More than 1 million of people lost their lives to this enemy already and more lives are claimed daily due to complications caused by the disease. Economies and different sectors, which are essential for basic living are also impacted hugely. Therefore, it is crucial to break the medical information to non-medical personnel. This will enhance adequate measures to prevent further damages to lives. Suffice it to say that, the need to shed more light on the fundamentals of this disease and to dispel the many conspiracy theories associated with the pandemic to the non-medical personnel will go a long way in saving many precious lives and also have a minor impact on the socio-econimic activities of the world.

2. History of SARS-CoV-2 Pandemic

On the 12th December 2019, initial cases of COVID-19 were discovered in Wuhan, a province in China. However, the origins of the pandemic of the unknown acute respiratory tract infection has no scientific proof as speculations related it to the seafood market in Wuhan. Despite the studies whose conclusions stood as the potential reservoir of SARS-CoV-2, until today there is no scientific evidence that, the virus is contracted from the seafood market [8]. In addition, based on the virus's genome sequencing that gave 96.2% overall genome sequence similarity between this novel virus and Bat CoV RaTG13, thus making it fit to share same possible ancestors. It is important to note that, bats are not found in this seafood market in Wuhan. Furthermore, protein sequence alignment and phylogenetic analysis proved possible alternative intermediate hosts, such as pangolins, snakes and turtles. This is based on the similarities of receptors that are observed in many of these species [9].

3. Novel SARS-CoV-2 Virus

To many, the SARS-CoV-2 causing COVID-19 is totally a new virus. However, this is just the newest form emerging from the coronavirus (CoVs) family and the first coronavirus to be responsible for a global pandemic. There are two other CoVs that emerged as novel coronavirus, causing epidemics and claimed lives previously. SARS-CoV, which emerged in china killed 916 out of 8422 confirmed cases (10.87%) and spread across 32 countries. MERS-CoV infected 2496 and claimed 868 (34.77%) lives while crossing boundaries of 27 different countries. Prior to these two super-spreading viruses, coronaviruses were studied as having a low potential for community transmission. The big family of CoVs are divided into four genera alpha, beta, gamma and delta (α−/β−/γ−/δ-CoV). The first two infect mammals including humans and the last two are found to infect birds. Prior to this novel β-SARS-CoV-2, six CoVs have been identified and apart from the β-CoVs, SARS-CoV and MERS-CoV that caused potentially fatal respiratory tract infections, low pathogenicity induced CoVs strains that caused mild symptoms, very similar to common cold were identified. If interest will rise on studying coranviruses, these are α-CoVs HCoV-229E and HCoV-NL63, and β-CoVs HCoV-HKU1 and HCoV-OC43 [10].

The newest member of the family, that is devastating the world, started at the end of 2019 through 2020 and now has gained a pandemic status. This is affecting daily activities of living and causing socio-economic crises while claiming lives of many is called severe acute respiratory syndrome virus 2 or SARS-CoV-2 and it was first discovered in a city called Wuhan in central China. The outbreak occurred exactly when the world's largest migration (Chinese lunar new year spring festival) was happening. Meaning extreme high air and train traffics came along with the virus [11]. That is the reason behind its rapid spread across the globe and despite low fatality compared to diseases caused by both SARS-CoV and MERS-CoV. As of April 21st according to worldometer, the virus had claimed the lives of 170,439 and infected 2,481,528 globally. While the recovery rate is 79% and the death rate is 21% making a case fatality rate of 0.069%. It is important to note that, these figures might not directly represent the true picture of the fatality of the virus as

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the data is only based on cases that received an official diagnosis. Some of the asymptomatic cases would never present to a health care facility for diagnosis, therefore they will not be part of the statistics.

The scientific evidences have gathered that this novel coronavirus is more contagious compared to its other family members. In addition, it has diverse epidemiological and biological characteristics, which makes it possible to infect many people in a short duration of time[11]. The virus is enveloped non-segmented positive-sense RNA virus (subgenus sarbecovirus, Orthocoronavirinae subfamily).

4. The Taxonomy of SARS-CoV-2 and COVID-19

On the 11th February, 2020 WHO officially named the disease caused by this novel virus as coronavirus disease 2019 (COVID-19). The virus is named as Severe acute respiratory syndrome virus 2 or SARS-CoV-2 by the Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses (ICTV) due to its 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV [11]. The word *coronam* is the Latin term for crown, due to the presence of spike glycoproteins on the envelope in the subfamily *Orthocoronavirinae* of the *Coronaviridae* family (order *Nidovirales*). According to WHO, it is important to name diseases to enable discussions on prevention, spread and transmissibility, severity and treatment. And also these names were chosen to avoid stigmatizing the virus's origin in terms of geography, populations or animal associations.

5. A Brief Summary on the Pathophysiology of SARS-CoV-2

COVID-19 infect the body by holding onto receptors and entering healthy cells. Receptors are proteins on the surface or inside of cells which is able to recognize chemical substances, viruses and drugs for example). Once inside the cell, the virus makes copies of itself and multiplies throughout the cells in the body by making new proteins leading to formation of new viruses. The novel coronavirus uses the same receptor as that of the SARS-CoV, and mainly spreads through the respiratory tract it can gain entry into the body through the eyes, nose, or mouth. It then enters the cells by using its spikey surface proteins to attach to receptors on normal cells, especially those in the airways. The angiotensin-converting enzyme 2 (ACE2) found in abundance in the human's lower respiratory tract, is known as the cell receptor for SARS-CoV which causes SARS [12] and also regulates both cross-species and human-to-human transmission [13].

This viral entry was reported, when they isolated COVID-19 from the bronchoalveolar lavage fluid, and they confirmed that the SARS-CoV-2 uses the same cellular entery mechanism (ACE2) as SARS-CoV [14]. The CoVs S protein mediates the entery of the virus into host cells [15], then receptor-binding domain (RBD) within the S1 domain facilitate binding to host cell receptor and S2 domain facilitate the viral fusion between host cell membrane and viral membrane which is an essential part in the entery of CoVs into host cells [16,17]. Once inside, the coronavirus hijacks the healthy cells and takes over command. Eventually, they kill some of the healthy cells and new viruses will infect other healthy cells and this goes on and on since it is in control of the genetic mechanism of the cells.

As the infection reaches the lower respiratory system, including the lungs, breathing becomes difficult. This is when more serious medical problems can develop, problems like pneumonia. This makes the airways swell and the lungs fill with fluid. In the most severe cases, this fluid in the lungs can lead to acute respiratory distress syndrome, or ARDS. People with ARDS are usually already hospitalized. ARDS makes it difficult or impossible to breathe because the lungs are grossly inflamed making gas exchange with the breathing in of oxygen and expulsion of carbondioxide as a waste product difficult leading to suffocation of tissues. As fluid collects in the lungs, they carry less oxygen to the blood. That means the blood may not supply organs with enough oxygen to survive. This can cause organs like the kidneys, lungs, and liver to fail and stop working leading to multi organ failure and eventually death [16].

However, it is important to mention that not everyone who gets infected with COVID-19 will develop serious complications needing hospital admission and advanced medical attention. Asymptomatic and mild cases may need supportive treatment at home or at an isolation center.

6. The Genetic Make Up of SARS-CoV-2

This virus is an enveloped positive single-stranded RNA (ssRNA) from the coronavirus family. The open reading frame (ORF 1a/b) encodes 16 non-structure protiens (NSPs) and two-thirds of the viral RNA mianly located in the (ORF 1a/b). The rest of the viral genome encodes for essential structural protein such as spike (S) glycoprotein, matrix (M) protein, nucleocapsid (N) protein, small envelope (E) protein and several accessory proteins [13]. The virulent factor that enables SARS-CoV-2 to binds to host cells receptor angiotensin-converting enzyme (ACE2) and enter in the host cells is S glycoprotein. Receptor-

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binding domain (RBD); heptad repeat (HR) 1 and 2. What is yet to be clear until today, is the possible molecules facilitated membrane invagination for SARS-CoV-2 endocytosis. Like many "self and nonself" mechanisms occurring, host factors (Lower panel) influences susceptibility to infection and disease progression [19].

7. People Most Vulnerable to SARS-CoV-2

Risk factors for severe COVID-19 includes and is not limited to advanced age, immunocompromised state, diabetes, cardiovascular disease including hypertension, chronic pulmonary disease, chronickidney disease, liver disease, cancer and severe obesity [20]. Everyone is at risk but the groups mentioned with underlying health problems are at greater risk due to weak immune systems and dysfunctions in various organ systems of the body. Smoking, to date, has been assumed to be possibly associated with adverse disease prognosis, as extensive evidence has highlighted the negative impact of tobacco use on lung health and its causal association with a plethora of respiratory diseases [21]. Previous studies have shown that smokers are twice more likely than non-smokers to contract influenza and have more severe symptoms, while smokers were also noted to have higher mortality in the previous MERSCoV outbreak [22,23]. Smoking cigarettes increases viral receptors on the respiratory surface, which might explain the increase in deaths in smokers reported by early researches on the disease.

It is noteworthy that, infants and children have not been featured prominently in COVID-19 case statistics. Despite the global pandemic of COVID-19, the clinical patterns and epidemiological findings remain unclear, especially among these groups. According to reports on COVID-19 among Chinese children in Wuhan, compared to adults, children were less likely to be infected and to have a severe illness, but they are still at risk from this pandemic. A nationwide study of 2143 COVID-19 pediatric patients conducted between January and February 2020 by the Chinese Center for Disease Control and Prevention, reported that all children of all ages were susceptible to COVID-19 without significant gender difference. Moreover, the severity of clinical manifestation among children infected with SARS-CoV-2 was generally less severe compared to adult patients and infants that were vulnerable to infection [24].

Another analysis from China also saw that, children younger than 10 years account for only 1% of COVID-19 cases [25], similar to the proportion for SARS-CoV and MERS-CoV epidemics [26,27]. Infants and young children are typically at high risk for admission to hospital after respiratory tract infection with viruses such as respiratory syncytial virus and influenza virus. Immaturity of the respiratory tract and immune system is thought to contribute to severe viral respiratory disease in this age group [28]. Therefore, the absence of paediatric patients with COVID-19 has perplexed clinicians, epidemiologists, and scientists. Case definitions and management strategies for children are absent because of the limited number of paediatric patients with COVID-19.

Athough blood groups are not established biomarkers, based on existing studies, people with blood type A are at higher risk of infection compared to non-A blood groups while blood type O has a significant lower risk for infection and severity compared to non-O blood groups. Although the higher death rate are seen among elderly people and those with pre-existing health issues. A study conducted in Wuhan, China found that, those with type A blood group are more likely to die from COVID-19 [29].

8. Antibodies Against COVID-19

Based on the available scientific data, the evidence on COVID-19 induced immunity is limited. That is to say, whether any immunity would give long-lasting protection against the virus is yet to be clear. A woman in Japan was reported to have tested positive for the second time after been given all the clear and also in China SARS-CoV-2 positive men became positive for the second time [30]. Until we see different occurrences, it means that, there is possibility for reinfections and repeated rounds until there is a vaccine or a herd immunity is developed. Herd immunity is when 50% of the population got sick and recovered while developing antibodies against the viral antigen [31]. Again since there is a knowledge gap surrounding the entire science of this virus, not everything said or speculated is uncertain. According to Ira Longini at the University of Florida, there is an evidence centered on anecdotal reinfection. But he added, that "we really don't know".

A breakthrough was seen on mouse model study conducted by the Chinese Academy of Medical Sciences in Beijing after exposing four rhesus macaques to the virus, they came up with the conclusion that, mice have antibodies to the virus in their bloodstream. And they tried to re-infect them but it fails, meaning the animals are immune. However, this might not necessary be a long-term induce imunity. For example, some people develop common cold immunity but this induced immunity are most often relatively short-lived. On the contrary to this as per humans, researchers at the London School of Hygiene & Tropical Medicine (LSHTM) reported that there is an increasing convincing evidence that, infection with SARS-CoV-2 leads to an antibody response that is protective. Although they request more evidence, their stance is on

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antibody protection for life. That means, there will be no second experience for infection. However, everything we are learning about this virus is new and independent researchers are required in order to understand how protective the antibody response will be in the long-term. To sum of the issue of re-infecting, WHO warned against declaring recovered patients "risk free" since currently there is no evidence that people recovered from COVID-19 and have antibodies are protected from second infection.

9. Mother to Baby Transmission

According to the CDC, during pregnancy, the transmission of SARS-CoV to the fetus or the baby during delivery is still unknown. Although, no neonates born to positive mothers are seen to have COVID-19 or infected and tested positive for the virus. In such cases, which were a small number, the amniotic fluid or breastmilk was free of the virus [32]. Moreover, a very recent case report conducted by Chen Y, et al [33] described the clinical course of four live-born infants. These infants were born to pregnant women infected with the COVID-19. Due to concerns about symptomatic maternal infection, three of the four women had a Cesarean (C) section and the for the fourth infant, his birth was through a vaginal delivery. None of the four newborns developed COVID-19 infection [33]. Another recent study conducted by Chen et al in February 2020 in China, that involved nine pregnant women infected with SARS-CoV-2 and developed pneumonia. There was no reported evidence of verticle transmission of the virus from women infected with the novel coronavirus to their infants [34]. However, a new study conducted by Zeng et al [35] suggested that, vertical transmission of the virus from infected mother with COVID-19 to the fetus is possible.

10. Conspiracy on the Virus being Weaponized

Following the rumors that the virus might escaped from a high-security biochemical lab in Wuhan, China, experts used the e genome sequences made available by the Chinese to explore the origins of and evolution of SARS-CoV-2. Apparently, from the studies done by scientists around the globe, they could not find any proof that the virus is made in a laboratory or engineered. This is based on the public genome sequence data from SARS-CoV-2 and related viruses. The science behind is to analyze the genetic template for spike proteins, armatures on the outside of the virus that grabs and penetrate the outer walls of host cells.

Until now, we could not established scientific grounds as to the virus being weaponized although the levels of genetic similarity existing between SARS-CoV-2 and RaTG13 suggested no variant that caused the outbreak in humans by the latter. Almost half of the genome of the distinct lineage of SARS-CoV is within the betacoronavirus and this gives evidence that this novel coronavirus is not-mosaic [36].

The two important features of the protein spikes are the receptor-binding domain (RBD) and the cleavage site. RBD can be viewed as a male since it has a kind of grapping hook that grips onto the host cells and the cleavage site can be seen as a female with a molecular can opener that allows the virus to crack open and enter host cells. If someone was going to engineer a new virus as a pathogen, then the backbone or the molecular structure would be a known virus that can cause illness. However this virus has mutations in its RBD portion of the spike protein and a distinct molecular structure thus, this is enough to rule out laboroatory manipulations as a potential origin.

Although the quest to know the exact origin of this virus is ongoing and independent research groups were able to correlate results of SARS-CoV-2 β-coronavirus, with similar geneticmake up to bat coronavirus (Bat-SARSr-CoV RaTG13). The genome sequence of SARS-CoV-2 is 96.2% identical to a bat CoV RaTG13, whereas it shares 79.5% identity to SARS-CoV. The natural source of the virus orgin is suspected to be bat based on virus genome sequencing and SARS-CoV-2 might be transmitted from bats via unknown intermediate hosts to infect humans. The similarities found is the receptor, angiotensin-converting enzyme 2 (ACE2) is the same for SARS-CoV and they both dpread through respiratory mechanisms[11].

11. Mutations Occurring within SARS-CoV-2

A study conducted on the genetoype of SARS-CoV-2 in different patients in different provinces found that, the virus had mutated in different patients in China [37]. Another study on population genetic analysis of 103 SARS-CoV-2 genomes revealed two types; SARS-CoV-2 type L (~70%) and S type (~30%). The evolutionary more aggressive and contagious strains in L types are derived from S type [15]. The mutation occurring in the NSP2 and NSP3 confers the infectious capability and also differentiation mechanism of SARS-CoV-2. This form of mutation is crucial for therapeutic targets. However, the mutation in S1 spike protein is not affected in the sequences and hence the antigen that scientists are targeting for vaccine production is not affected. Most coronaviruses caused upper respiratory infections like

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common cold but of recent, fatal respiratory diseases and outbreak including the strain that causes COVID-19 has the potential to mutate. In fact, the early studies speculate that this virus is being caused by mutants from species spillover in Wuhan's wild animal market[38]. However, this begs for further studies that will bring in evidence based on experiments.

12. Expectations to See COVID-19 in the Future

With experience from SARS and MERS epidemics, the asymptomatic and pre-symptomatic transmission and the chances of gene viral mutations, if effective vaccines are not develop to win the battle, we are likely to face this outbreak again and perhaps in a different form or strain. Those receiving antiviral drugs should establish a complete elimination of the viral particles in the body. Failure for complete eradication will promote drug resistance that will lead to drawing back of therapeutic interventions back to the basics.

13. Conclusion

The global citizens must be reminded that in as much as we have suffered losses, pain and undending anxieties, one fundamental thing that should always be remembered is that, an outbreak of disease just like floods, storms and earthquakes as well are natural disasters. In essence, there should be no stigmamatization or discrimination. We need to come clean and plain at the right time for global scientific interventions. Both the medical institutions and the Governments should be honest and transparent so that we can win this war against the novel coronavirus by providing the right directions. WHO 2020 continues to advise on the importance of solidarity when it comes to fighting a common enemy and in containing any outbreaks, epidemics or pandemics, discilpine is key as to experts guidelines.

Everyone is affected either directly or indirectly even if you are not infected, the outbreak halted the global functions and everyone should strive to ensure that bad memories are never repeated. Esentially, we need to draw our resolution and work towards any similar enemy to the human race. It is a collective responsibility to fight against this virus in order to stop further spreading by providing the right information to the public. If we do not come together to fight to win the battle, we might not be lucky by be witnessing many countries with long-lasting sequela.

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REVIEW

Research Progress of Anti-tumor Active Ingredients in Dandelion

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ABSTRACT

As a traditional Chinese herb, dandelion, containing complicated active ingredients which includes polysaccharide, flavonoid, terpene, pigment, phytosterol, coumarin, organic acid and etc, plays significant roles in various physiological activities in organisms. The active ingredients generally interfere in signal transduction of cancer cells, regulate cell cycle and apoptotic protein expression, inhibit cancer cells proliferation and migration and etc, which effectively restrains tumor development and deterioration. This article summarizes the anti-tumor mechanism of five active ingredients in dandelion through paper reading which provides thoughts and references for anti-tumor research.

1. Introduction

Radiation in physics, various chemical carcinogens and biological factors could cause tumorigenesis [1-3]. 9.6 million people around the world were estimated to have died from cancers in 2018 according to WHO and 1 out of 6 deaths is due to cancer, globally. New cancer cases rose to 18.1 million in 2018 based on WHO data statistics. Anti-cancer research remains hot topic for decades, besides surgery, radiation, immunotherapy, hormone therapy, stem cell transplant, precision medicine and targeted therapy, chemotherapy is a traditional and major method which uses drugs to kill cancer cells, whereas the correlated disadvantages decreased the therapeutic effect [4-9]. Traditional Chinese herbs are being used to cure various diseases for thousand years in China, nowadays, effective ingredients extracted from herbs are being more and more popular in drug research, development and clinical trials [10-24].

Dandelion, perennial plant, belongs to taraxacum genus of asteraceae family, also known as Yellow flower, Huanghua DeDing, Milk grass and etc, in China [25]. There are more than 300 species and 2000 subspecies of taraxacum, globally, and among those 70 species are discovered in China [26,27]. Dandelion tastes bitter, sweet, cold and return to the liver and stomach due to traditional Chinese medicinal literature. Dandelion harboring multiple active ingredients includes polysaccharide, flavone, terpene, pigment, phytosterol, coumarin, organic acid and etc [28,29]. Active ingredients of dandelion function mainly in anti-tumors,

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antioxidation, boosting immunity and bacteriostatic [30]. In this paper we reviewed several active ingredients with anti-tumor effect in dandelion and aimed to provide new thoughts and references in anti-neoplastic research, treatment and antineoplastic agents development.

2. Active Ingredient in Dandelion

Dandelion possesses abundant of protein (18.8%), amino acid, carbohydrate vitamins and etc, and besides concentrations of calcium [31], phosphorus and iron elements are higher than common fruits and vegetables [28,32,33]. Dandelion contains various active ingredients, for instance, taraxacin, taraxasterol, saponin, caffeic acid, chlorogenic acid, flavonoid, polysaccharide, volatile oil, choline, inositol and etc [28,32,34]. In addition to the illustrated active ingredients above, the whole dandelion herb harbors amaroid, resin, synanthrin, pectin and etc [35,36]. β-sitosterol, stigmasterol, linoleic acid were identified in dandelion root, and xanthophyll, phylloquinone, γ-aminobutyric acid, sulfonyl amino acids, ornithine acid in dandelion leaf, and capretin, sarcochediol, lutein in dandelion blossom, and β-sitosterol, folate in pollen [28,29,37]. A total of 66 trace elements have been detected in dandelion and among those Cd, Cu, Zn, Fe, Mn and Mo essential trace elements are higher in contents [38] (Chinese paper with DOI: 10.3969/j. issn.1006-0111.2002.04.026). Dandelions contain up to 14.7 μg/100 g of selenium which is considered a rare anti-tumor active substance in human body (Chinese paper with DOI: 10.3969/j. issn.1008-1445.2015.01.009). Dandelions, as a scarce selenium-rich plant in nature, has high nutritional and medical value, and is a veritable plant for both medicine and food [39,40]. Dandelions as a traditional herb is widely used to treat inflammation, constipation, stomach diseases, scald, tumor prevention and treatment, etc, in China, and those may correlate to the contained active ingredients [28,41-43].

3. Anti-tumor Active Ingredients in Dandelion

3.1 Dandelion Polysaccharide

Dandelion polysaccharide is one of the active component extracted from the whole dandelion grass and mainly gathering in root [44-46]. Dandelion polysaccharide functions in anti-tumor, boosting immunity, decreasing blood sugar and lipid, antioxidant and anti-aging [44,45,47-51]. Clinical trials have proved good effect of dandelion polysaccharide on anti-tumor [52,53]. Dandelion polysaccharide could induce melanoma cells and leukemia cells (Jurkat) apoptosis through caspase-8 and cause no harm to normal cells [54,55].

3.2 Triterpenoid

Triterpenoids are widely distributed in plant kingdom and composed of 30 carbon atoms, polymerized to form six isoprene units [56]. Through promoting cell apoptosis, intervening cell signaling transduction and regulating cell apoptosis-related protein expression, triterpenoids realize anti-tumor effect [57-60]. Taraxerol and taraxeryl acetate both exhibit gastric cancer cell line AGS growth suppression, but taraxerol shows more significant in cell cycle arrest and apoptosis of AGS cell lines [61,62]. When taraxerol concentration reached 300 μmol/L and action time achieved 72 hours, AGS cell line growth inhibition rate attained 99.1%. Taraxerol inhibited cell cycle at G_2/M stage, thereby inhibiting AGS cells growth [62]. Shi segmented rat urine that were fed with dandelion extract with semi-prepared HPLC and divided into 11 subsections. The urine subsections were applied to MTT testing, and potential active sections were analyzed through UPLC-MS, and lupeol and taraxerol were detected in the subsections (Chinese paper with DOI:10.3724/sp.j.1123.2013.11010).

3.3 β-sitosterol

Phytosterols are kinds of active ingredients in plant cell membrane which are structurally similar with animal sterol, such as cholesterol. Dandelion β-sitosterol belongs to phytosterols and plays significant roles in antagonizing cancers [63]. Previous studies had proved sitosterol inhibited lung cancer A549 and NCI-H460 cells growth through a dose-dependent manner and blocked cell cycle in G_2/M phase [64-66]. Western Blot results showed expressions of tumor suppressive protein P53 and pro-apoptotic protein Bax increased along with β-sitosterol concentration, whereas expression of anti-apoptotic protein Bcl-2 decreased gradually (Chinese paper with DOI: 10.3969/j.issn.1673-4130.2016.07.001). Tumor cells experienced some morphological changes, such as density reduction, nuclear shrinkage and apoptotic body emerging after Dandelion β-sitosterol treatment [64].

3.4 Flavonoid

Flavonoid generally refers to a series of compounds formed by interconnecting two phenolic hydroxyl benzene rings through a central three-carbon chain, and its basic parent nucleus is 2-phenylchromogenic ketone [67,68]. Flavonoids are a large class of secondary metabolites having a structure based on or similar to flavone which are secreted by plant and fungus [69]. Flavonoid, harboring various physiological activities, attracts much

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more attention, globally. Anti-cancer mechanism of flavonoids includes inhibiting the proliferation of cancer cells and inducing apoptosis, inhibiting cancer cells migration, inhibiting VEGF activation and thus inhibiting neovascularization [70-73]. Dandelion flavone suppressed esophageal cancer cell line TE-1 growth, and low concentration of flavone in the dandelion extract could not produce cell growth inhibition, but when dandelion flavone concentration reached to 80 μg/mL, inhibition rate of TE-1 growth attaining maximum that was 54.2% (A Chinese maser thesis with DOI: CNKI: CDMD:2.1016.215206). Anti-tumor effect of dandelion flavone was significant in cellular level *in vitro*, but not in human trails and animal model. The reason might be that dandelion flavone could not enter the circulatory system completely cause of dual barrier of small intestine and liver, leading to low bioavailability of flavonoids (a Chinese paper with DOI: 10.3969/j.issn.1007-8517.2009.22.001).

3.5 Organic Acid Compounds

The most common organic acids are carboxylic acids and widely distributed in animal, plant, and microbial sources, whose acidity is derived from the carboxyl group (-COOH) [74-76]. Dandelion organic acids mainly include chlorogenic acid, caffeic acid, ferulic acid, and etc [68,77]. Gallic acid can inhibit gastric cancer cells metastasis and invasive growth [78,79]. Studies have shown that chlorogenic acid has an inhibitory effect on human nasopharyngeal carcinoma cell line CNE-1 by activating tumor suppressor genes P27 and P16 and inhibiting the expression of cyclin D1 (a Chinese paper with DOI:10.7652/jdyxb201406022). Yoon found that chicory acid may play an important role in inducing apoptosis which worked as a novel TRAIL sensitizer for cancer cells [80].

4. Pharmacological Research of Dandelion

Modern pharmacological studies have shown that 50% ethanol reflux extracts of dandelion dry plants can induce breast cancer cells arresting at G_2/M stage and cell apoptosis through endoplasmic reticulum stress [52,81]. Researches proved that dandelion dried herbs decocted extracts exhibited anti-tumor properties and reduced liver cancer cell line Hep G2 survival rate about 26%, whereas tumor necrosis factor (TNF-α) and interleukin (IL-1α) increased significantly [58]. Dandelion whole grass decoction extraction had significant inhibitory effects on the proliferation of hepatocellular carcinoma cells and colorectal cancer Lovo cells *in vitro*, with inhibition rates of 23.34% and 30.33%, respectively, suggesting that they may have certain application value in cancer treatment (A Chinese paper with DOI: 10.3969/j.issn.1004-2113.2005.04.010).

Dandelion whole herb decoction extract has a broad spectrum of bacteriostasis, including staphylococcus, streptococcus pneumoniae, beta hemolytic streptococcus, enterococcus, E. coli, klebsiella pneumoniae, sewer enterobacter, citrate coli, pseudomonas aeruginosa, h. influenzae, Branhamellacatarrhalis, and etc [48, 82, 83] (A Chinese paper with DOI: CNKI:SUN:ZWZX.0.2009-11-015). Dandelion extract had been used to treat skin diseases, clinically [84,85]. Modern pharmacological studies have shown that dandelion extract has certain effects on the gastrointestinal tract, mainly between the stomach and duodenum [32,70,86]. Previous studies demonstrated that dandelion extract could inhibit Helicobacter pylori (Hp) infection and then reduced gastric pain (A Chinese paper with DOI: 10.3969/j.issn.1000-7369.2011.06.078). Dandelion extracts had significant inhibitory effect on gastric acid secretion induced by histamine, penta-peptide and Carbamyl choline [62,87]. Dandelion had vital effect in gastric ulcer mucosal inflammation and erosion treatment [87].

Dandelion extract improves T-lymphocyte activity and enhances macrophage phagocytosis index while dandelion polysaccharide promotes spleen and thymus growth and development which strengthens immune function in mice [88]. Dandelion extract could suppress glucosidase activity and reduce blood glucose in mice, therefore improving its immune function (A Chinese paper with DOI: 10.15889/j.issn.1002-1302.2016.08.005). Besides, dandelion extract holds strong oxygen radical scavenging activity and anti-inflammatory activity [44,50,89-91].

5. Conclusion

Dandelion, as a kind of traditional Chinese medicine, has little toxic and side effects and high medicinal value which is widely used clinically in China (plenty of research papers in Chinese). The medicinal effect of dandelion may be due to the contained active ingredients. Dandelion possesses anti-cancer effect and the mechanism mainly includes interfering cell signal transduction, regulating expression of apoptosis-related proteins, suppressing carcinoma cells proliferation and migration, inhibition of angiogenesis, and so on [47,52,73,92,93]. To date, researches mainly focus on anti-cancer effect of dandelion whole grass extract which contains polysaccharides, flavones, organic acids, triterpenes, sterols and other active components [28,41,94,95]. However, the specific active components of extracts from different parts of dandelion have hardly been investigated. Therefore, it is great value to analyze and separate the anti-cancer active components of extracts from various parts of dandelion. Researches and developing of drugs has stepped into a new stage. Dandelion, as a

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natural drug, has a good research prospect, and development and utilization of dandelion active ingredient is of great scientific significance for anti-tumor research.

Conflict of Interests

The authors declare no conflict of interests.

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REVIEW

Nursing Care of a Case of Mediastinal Tumor Resection Combined with Postoperative Thoracic Hemorrhage after Video-assisted Thoracoscopic Surgery (VATS)

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ABSTRACT

Objective: To summarize the nursing experience of a patient with postoperative intrathoracic hemorrhage after thoracoscopic-assisted resection of the right upper mediastinal tumor through the original incision. **Methods:** Summarize the main points of nursing care of postoperative intrathoracic hemorrhage after thoracoscopic mediastinal surgery, including observation and nursing when internal hemorrhage occurs after operation, respiratory management, activity management and pain management measures. **Result:** After careful care, the patient recovered and discharged smoothly. **Conclusion:** It is particularly important to observe the overall observation and take timely corresponding nursing measures for patients with intrathoracic hemorrhage after thoracoscopic mediastinal surgery.

1. Introduction

Mediastinal tumors are a kind of thoracic tumors. Among them, mediastinal neurogenic tumors are one of the common mediastinal tumors, about 19-39% of mediastinal tumors [1], and most of them are benign. The treatment methods are mostly surgery, and the prognosis are better. Thoracic tumors have a higher risk of thoracotomy and are highly traumatic. Postoperative patients are prone to multiple complications. Postoperative intrathoracic hemorrhage is a common and more serious complication, about 1.9%, and the mortality rate after hemorrhage is about 4.7% [2]. Compared with traditional thoracotomy surgery, thoracoscopic surgery has obvious advantages in reducing surgical trauma and promoting postoperative recovery [3], and the postoperative intrathoracic hemorrhage rate is about 0.5% [4]. In the treatment of mediastinal tumors, thoracoscopic surgery is the gold standard for the treatment of benign neurogenic tumors of the mediastinum [5]. On January 2, 2020, a patient with intrathoracic hemorrhage after thoracoscopic-assisted resection of the upper right mediastinal tumor with the original incision was admitted to our department. After careful treatment and care, he was discharged from

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the hospital on January 23, 2020. The report is as follows:

Clinical Data

The patient, a male, 21 years old, underwent mediastinal tumor resection in Beijing Children's Hospital in 2005 (7 years old). Postoperative pathology showed posterior mediastinal schwannoma. Re-examination of chest CT at the Second Hospital of Daqing City on December 20, 2019 showed that there was a slight density of nodules in the posterior mediastinum, and the possibility of tumor recurrence was considered based on the medical history. On January 2, 2020, it was admitted to our department with mediastinal tumor. The enhanced CT on admission showed that the posterior mediastinum showed round-like nodules with a clear border, about 2.4*2.0cm in size and 3.6cm in length. The atypical veins were compressed and moved forward, and the anterior edge of the 5 thoracic vertebrae was sclerotic. There were no clear nodules or consolidation in both lungs and chest cavity. Complete the examination, and under general anesthesia on January 6, 2020, the "thoracoscopic-assisted original incision right upper mediastinal tumor resection" was performed. The operation went smoothly. After the operation, a closed thoracic drainage tube was placed at the mid-axillary line of the 8th intercostal space to drain fluid. A closed thoracic drainage tube is placed at the mid-axillary intercostal line to induce air. About 190ml of thoracic drainage fluid was drawn out at 14 hours postoperatively. 550ml of bright red fluid was drawn from the 8th intercostal drainage tube after the patient got out of bed from 14:00 to 16:00 on the first day after surgery. Blood pressure 108/67mmhg, HR 97 beats/min, complexion Pale, clammy limbs, patient complained of no discomfort. Immediately give 2 units of Agkistrodon acutus hemagglutinin + 0.9% sodium chloride injection 50ml intravenously, and apply chest strap compression bandage. The patient's hemoglobin dropped to 119g/L (at 07:00 on the same day, 136g/L)), he was asked to stay in bed, and 330ml of red liquid was drawn out again within 3 hours from 16:00 to 19:00. The patient's bleeding volume reached 1070ml on the first postoperative day. He was treated with hemostatic and fluid rehydration treatment, and the later drainage volume stabilized. The drainage tube was indwelled for 17 days after the operation, and the drainage fluid was about 150ml/d on the 2-17 day after the operation. The patient recovered well after careful care in our department and was discharged from the hospital on January 23, 2020.

2. Nursing

2.1 Observation and Nursing of Postoperative Intrathoracic Hemorrhage

Studies have shown that if the drainage volume is more than 200 ml/h, it may be active bleeding for more than 3 hours [6]. In addition, the expert consensus on the prevention and treatment of bleeding during the perioperative period of thoracic surgery indicated that the bleeding volume reached 500ml at 24 hours after operation, which means that the risk of active bleeding is higher [7]. The main causes of postoperative bleeding after mediastinal surgery include: large wounds in the chest surgery, adhesions between the anatomical position of the posterior mediastinumal tumor and the surrounding tissues and the surface of the lungs. The separation process is likely to cause large-scale capillary damage and severe capillary bleeding after surgery. After the adhesion of the pleural surface is peeled off, the bleeding is not completely stopped, and the negative pressure in the chest is restored after the chest is closed, and the blood can continue to ooze; the effect of electrocoagulation is poor, and the vigorous activity after the operation of the eschar can cause bleeding or large area of blood [8].

2.1.1 Closely Observe the Patient's Vital Signs

When the patient develops active internal bleeding, immediately monitor the patient's vital signs, pay attention to changes in blood pressure, heart rate, and respiration, and be alert to hypovolemic shock due to excessive blood loss. The shock index can estimate the patient's bleeding earlier The degree of shock and shock are important indicators for early observation of bleeding [9]. While monitoring vital signs, record blood pressure and heart rate every 5-10 minutes, and calculate shock index (shock index=heart rate/systolic blood pressure, normal value is 0.5-0.8) to assess the degree of blood loss. 1.0-1.5 means mild shock (20-30% blood loss), 1.5-2.0 means moderate shock (30-50% blood loss), and >2.0 means severe shock (blood loss>50%) [10-11].

2.1.2 Be Alert to Hypovolemic Shock

Hypovolemia triggers a series of pathophysiological reactions in the body's various system organs, which can lead to insufficient tissue perfusion, reduced cardiac output, cell metabolism disorders and functional impairment, and even hypovolemic shock, which seriously threatens the lives of patients.

(1) Observe skin changes: hypovolemia leads to the excitement of the sympathetic nerve-adrenal axis,

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the release of catecholamine hormones increases and selectively shrinks the skin, muscles and visceral blood vessels. The peripheral blood vessels are first contracted to increase the amount of blood returned to the heart. The patient has pale skin, clammy, cyanosis, or insufficient capillary filling, reflecting the patient's insufficient circulating blood volume and insufficient peripheral tissue perfusion, suggesting that there may have been bleeding and hypovolemia. Immediately assist in bed rest, take the concave position, rub the body with hot water, add quilts to keep warm, and help the patient drink hot water. And report to the superior nurse and doctor for further treatment.

(2) Observe changes in urine output: Hypovolemia will excite the renin-angiotensin II-aldosterone system, strengthen the reabsorption of sodium and water in the renal tubules, reduce urine, and preserve body fluids. Normal adult urine volume should be more than 30ml/h. If it is lower than this, it should be considered whether there is bleeding. If the patient's urine volume is less than 25ml/h, it proves that the bleeding volume is large and shock may exist. Ask about the patient's intake and output status. The patient is completely anuritic from 10 am to 16 am. Two venous accesses are quickly established. During the infusion process, the infusion speed is adjusted according to the patient's urine output and the type of fluid input, while the hourly urine output is recorded. Give dietary education, assist the patient to take a small amount of oral rehydration and drink more than 2000ml.

2.1.3 Closely Observe and Record Changes in the Color, Nature, Amount and Temperature of the Drainage Fluid

(1) The patient's drainage fluid is bright red, the temperature of the drainage tube is close to the body temperature, and a small amount of mist appears in the drainage tube, indicating that active bleeding in the chest cavity is more likely. Observe and record the changes in the color, nature, and amount of the drainage fluid every 30 minutes, and closely monitor the bleeding of patients [12].

(2) Check whether the drainage tube is properly fixed, keep the drainage tube unobstructed, squeeze the drainage tube regularly, and squeeze the thoracic drainage tube once every 30min to 60min to avoid clot blocking the tube and cause hemorrhage and affect clinical judgment. The squeeze method is as follows: one hand blocks the drainage tube at the proximal end of the chest cavity, and the other hand holds the drainage tube tightly and squeezes it toward the thoracic bottle with thenar force; hold the drainage tube with both hands about 10-15cm from the chest cavity exit , The hands are connected back and forth, the back hand squeezes the drainage tube, the front hand quickly squeezes the drainage tube.

2.1.4 Pay Attention to Patient Examination Results

In patients with postoperative intrathoracic hemorrhage, CT examination generally indicates an increase in intrapleural effusion; the hemoglobin in routine blood examination is lower than normal, and every 10 g/L drop in Hb, the cumulative blood loss is about 400-500 ml, Hb<70/L, when, It suggests that the amount of bleeding is large [4]; the composition of the drainage fluid for routine examination of pleural fluid is similar to that of whole blood, or hemoglobin ≥50g/L [13].

Follow the doctor's instructions to check the patient's blood routine urgently, assist in taking CT of the chest at the bedside, and follow up the auxiliary examination results in time to further confirm the diagnosis.

2.2 Other Care

2.2.1 Activity Management

Due to the pain and the wound of the laparoscopic surgery is in the patient's third intercostal space, which is close to the shoulder joint, the patient is afraid of activities affecting wound healing and other factors. Studies have shown that actively or actively assisting shoulder movements can help prevent postoperative complications [14]. Proper limb exercises help prevent deep vein thrombosis and reduce complications such as respiratory tract infections [15]. When patients have heavy bleeding, they should rest in bed, avoid large-scale activities, and focus on bed activities.

(1) Upper extremity exercise: Instruct patients to exercise through bilateral arm abduction, uplift, and bilateral shoulder joint forward and backward rotation. At the same time, care should be taken to avoid pulling the chest tube and other drainage lines, and proceed gradually until the preoperative mobility is restored.

(2) Lower extremity exercise: Instruct the patient to exercise the lower extremities on the bed, such as ankle pump exercise, the lower extremities take turns in flexion, extension, and elevation, knees bend and feet push the bed to raise the hips, etc., 3-4 times a day, 10-each time 15 min.

2.2.2 Respiratory Function Exercise

(1) Give pillows and raise the head of the bed 30°, which not only facilitates breathing, but also helps to

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reduce wound tension and prevent the wound from bleeding again due to excessive tension.

(2) Instruct patients to exercise their respiratory function. Methods such as deep breathing and abdominal breathing can help reduce the rate of lung infection in patients after chest surgery [16]. Decreased lung function is also a major factor in the occurrence of complications after minimally invasive lung surgery [17]. Increasing the postoperative abnormally reduced functional residual capacity, which is the lung volume, can effectively reduce the occurrence of postoperative pulmonary complications, and the effective measures for exercise include deep inhalation exercises. Instruct patients to take deep breaths and abdominal breathing 4-6 times a day, 20 minutes each time; a three-chamber breathing trainer can also be used, 10-15 minutes each time, 4-6 times a day. How to use: Let the patient inhale deeply to generate upward airflow in the air cavity. When the airflow velocity is large enough, the measuring buoy will rise. The breathing exerciser adopts a similar blocking structure to form breathing resistance, so that the patient's lungs are fully expanded when breathing [18].

(3) For patients with internal hemorrhage, blood vessels may have ruptured or Jiaojia has fallen off in the chest cavity. Instruct patients to avoid coughing and sputum as much as possible, use cough medicine appropriately, and use negative pressure suction for patients with more sputum.

2.2.3 Pain Management

Bleeding can easily cause anxiety and fear in patients and increase the risk of pain [19]. The pain can also cause tension, cramps, etc., which may also increase the bleeding tendency. Appropriate use of analgesics to relieve pain is conducive to rapid recovery of patients after surgery. The APS/ASRA/ASA guidelines suggest that various modes or drug analgesia are recommended for postoperative pain in adults, and patient-controlled analgesia is recommended [20]. The SFAR postoperative analgesia guidelines recommend the prescribing of strong tablets (morphine). Or oxycodone) is used orally in patients, and type 2 cyclooxygenase inhibitors can be used in combination with no contraindications [21].

(1) Pay attention to the psychological changes of patients, comfort the patients in time, and do a good job in educating the patients' family members to reduce the psychological pressure of the patients. Avoid anxiety and fear caused by bleeding and increase pain.

(2) Give patients postoperative use of self-controlled analgesia pump, the duration is 48-72h, and self-regulate according to their own conditions. Routine postoperative administration of parecoxib sodium intravenous injection + paracetamol and oxycodone tablets orally.

(3) Use chest and abdomen straps to fix the chest of the patient, pressurize the bandage, and reduce the wound pain caused by the increase in tension caused by the activity.

3. Summary

The mortality rate of postoperative bleeding is significantly higher than that of intraoperative bleeding [22], and with the development of surgical technology, the application of laparoscopic surgery in thoracic surgery gradually dominates, and the nursing requirements for laparoscopic surgery have become more stringent. Laparoscopic surgery has a small wound, the wound exudation is not obvious, and postoperative bleeding is difficult to find. This requires our nurses to observe carefully during the nursing process, master the signs of internal bleeding or active bleeding, detect them early, determine them in time, and take corresponding nursing measures in time to cooperate with the doctor in the next operation and treatment. Once discovered not in time, the loss to the patient, the follow-up treatment and the degree of care will be more complicated. Therefore, early detection, early determination, and early treatment are the basic requirements for nurses.

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ARTICLE

Lead to Elevate the Temperature and Speed of Emergency Rescue and Nursing Care of Common Carotid Artery Rupture and Massive Hemorrhage after Operation of Typical Esophageal Cancer

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ABSTRACT

Objective: Objective To explore the first aid and nursing of patients with anastomotic fistula after radical resection of esophagus carcinoma complicated with major carotid hemorrhage. **Methods:** The clinical data of anastomotic fistula complicated with carotid artery rupture and massive hemorrhage after radical resection of typical esophageal carcinoma were analyzed and summarized. **Results:** Through the close cooperation of medical care, the rescue was successful. **Conclusion:** Earlier prevention observation, raising first aid consciousness and actively cooperating with doctors can improve the success rate of rescue.

1. Introduction

Esophageal cancer is one of primary malignant tumors in our country, "Global Cancer Statistics 2018" showed esophageal malignant tumor is east Asian characteristics, China accounts for more than 50% of new cases each year [1].The latest figures show 2019 esophageal cancer is one of the major cancer in our country is located in the top five, Incidence as high as 6.26%, Mortality rate as high as 8.04%. At present, the treatment of esophageal cancer is mainly based on operation, combined with radiotherapy and chemotherapy [2]. Anastomotic fistula is one of the most serious complications after esophageal cancer operation. The incidence rate of anastomotic fistula after esophageal cancer operation range from 8% to 24%, and the mortality rate is 11.0% to 35.7% [3]. The incidence of intrathoracic anastomotic leakage was 3% to 5%, and that of cervical anastomotic leakage was 5% to 14% [4]. Carotid artery rupture caused by anastomotic fistula is a kind of rare but extremely dangerous emergency. Rescue can save the patient's life in time, which can easily lead to hemiplegia or even death.

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In November 2019, our department admitted a case of carotid rupture and massive hemorrhage caused by anastomotic fistula in 52 days after operation for esophageal cancer. Summarized the nursing of anastomotic fistula and rescue experience of common carotid artery rupture and hemorrhage for esophageal cancer, improved rescue success rate and reduced mortality rate. The nursing experience is reported as follows:

2. Clinical Data

Male, 54 years old, with concurrent radiochemotherapy for esophageal mid - thoracic squamous cell carcinoma (radiotherapy was started in August 2019, with a total of 22f radiotherapy dose: 95%PGTV 47.3Gy/2.15Gy/22f, PTV 39.6Gy/1.8Gy/22f; During one cycle of simultaneous chemotherapy with capecitabine plus nedaplatin, capecitabine 1500 mg/m^2, nedaplatin 25 mg/m^2 q1w^2), Checked in to our department in November 2019 for surgical treatment. "Thoracolaparoscopic combined three - incision esophageal cancer resection by gastric replacement esophagocervical anastomosis" under general anesthesia on November 26,2019, following a complete assessment of the relevant examination, On day 8, the neck incision was red and swollen, The results of endoscopy showed that the anastomotic stoma was in deep depression and the diagnosis of cervical anastomotic stoma fistula. the neck wound is opened and the fistula bag is connected with a negative pressure bottle to be fully drained, a large amount of pyogenetic odor secretion is led out, and 50ml of metronidazole is continuously washed and changed, and the secretion is cultured into pseudomonas aeruginosa and oral streptococcus. Amikacin + vancomycin anti-infection treatment according to drug sensitivity, supplementing nutritional support such as albumin, high vigilance for anastomotic abscess erosion of neck blood vessels, Postoperative day 52, After severe coughing, the common carotid artery ruptured and hemorrhaged during medical ward rounds, electrocardiogram monitoring, high-flow oxygen inhalation, establishment of double venous pathway, intravenous drip of pituitrin, methylprednone and Ringer's fluid, the bedside trachea is incised and the trachea intubation is indwelled and the continuous breathing balloon is used for assisting breathing and removing blood clots, After being signed by the family, the emergency general anesthesia was immediately sent to the operating room for "exploratory disconnection of the left common carotid artery of the median splitting sternum + cervical esophagus fistula + thoracic gastric fistula + debridement and drainage" and transferred to ICU for treatment after the operation.

3. Rescue Preparation

(1) Item preparation. For patients with long-term anastomotic fistula non-healing and increased fluid leakage, prepare for bleeding rescue. Negative pressure aspirator, oxygen, shadowless lamp, tracheotomy bag, tracheal intubation box (containing respiratory balloon, laryngoscope, tracheal intubation belt air bag, intubation tube core), first aid medicine, etc. should be provided beside the bed. And make sure it's in good condition in case of urgent need.

(2) Judging whether it is carotid bleeding is the key to rescue. The carotid artery hemorrhage is turbulent and manifested as a large amount of blood gushing out from the nasal cavity, mouth, airway and wound. Once the carotid artery hemorrhage is diagnosed, the first means of rescue is to press and stop the bleeding, the method is as follows: opening the wound, Directly place your fingers on the artery (preferably on the upper and lower ends of the hemorrhagic site) for compression, with the best force to block blood flow, and avoid pressing the trachea too hard to affect breathing.

(3) Keep the airway unobstructed and prevent asphyxiation: assist the patient to take the side lying position of the patient with one side of the head to help the blood lead out, encourage the patient to cough up the blood at any time without force, tell the patient to maintain the normal breathing frequency not to hold breath, Prepare tongue depressor, mouth opener, aspirator, etc. If blood clot still cannot be discharged, use suction tube to aspirate, and prepare and explain the items for tracheotomy or tracheal intubation.

(4) Assisting tracheotomy: assisting the patient to take the supine position, raising the shoulder by about 10cm, making the head as far back as possible, facilitating exposure of the trachea, selecting a suitable low-pressure airbag catheter according to the age and body type of the patient, generally selecting a catheter of 7.5-8mm for adults, the nurse stands on the left side of the patient, holds a sputum suction tube to clean the blood of the operation field and blood clots of the oral and nasal cavity at any time, puts the tracheal cannula into the trachea after the tracheal incision, inflates the catheter air sac, the suction tube is inserted into the trachea through the trachea to absorb the blood clots, Connect the respiratory balloon to continuously positive pressure ventilation, the tracheal sleeve is fixed to the neck by a lace, elastic to extend into 1 finger is appropriate, a piece of vaseline gauze is plugged under the skin to stop bleeding, and two pieces of open gauze are used between the wound and the sleeve [5].

(5) Closely observe the changes of vital signs, state of consciousness, complexion, temperature of limbs, urinary

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volume, ECG monitoring, high-flow oxygen uptake, keep warm.

(6) Establish more than 2 venous channels, apply hemostasis, replenish blood volume, boost blood pressure, vasoactive drugs, draw cross-match blood, inform blood bank to prepare blood. Prepare oil gauze, gauze, gauze wet with adrenaline to give compression hemostasis, contact the operating room, anesthesiology department, ICU to prepare.

(7) Do a good psychological care, comfort patients and family members, tell them not to be nervous, cooperate with rescue.

4. Discussion

4.1 Cause Analysis of Bleeding

(1) The left side of the common carotid artery originates from the aortic arch, the anterior lower segment of the common carotid artery is covered by the sternocleidomastoid muscle, the medial side is adjacent to the esophagus, the trachea, the larynx and the thyroid, and the anterior edge of the sternocleidomastoid muscle is cut in the neck for radical esophagectomy, Cut the skin subcutaneous tissue and platysma muscle, draw the sternocleidomastoid muscle and the cervical vascular sheath outwards, cut the esophagus in the neck, lift the tubular gastric autoesophageal bed to the neck, and perform mechanical anastomosis with the normal esophagus in the neck [6]. Postoperative cervical anastomotic fistula may result in prolonged immersion of the carotid artery in saliva, gastric juice or a large amount of exudate, and continued erosion of the artery wall.

(2) Preoperative radiochemotherapy significantly increased the incidence of local tissue dysfunction, wound infection, tissue necrosis and anastomotic fistula. At the same time, radiotherapy also directly damaged arteries, leading to thrombosis and atherosclerosis, which significantly reduced the intensity of arterial wall [7].

(3) Due to the consumption of diseases, surgical trauma, postoperative fasting, nutritional insufficiency, increased metabolic consumption, poor vascular condition and inadequate peripheral fluid, the malnourishment of tumor patients resulted in malnutrition, which was not conducive to the healing of anastomotic fistula.

4.2 Prevention of Bbleeding

Long-term erosion of carotid artery by anastomotic fistula is the main cause of hemorrhage, and the causes of anastomotic fistula are complex, which are related to operation, operation, gastric stump and esophageal blood circulation, thoracic infection and systemic nutritional support [8]. Early improvement of nutritional status, prevention of infection and constipation, promote the healing of anastomosis is of great significance to prevent carotid hemorrhage [9].

(1) Nutritional support: Esophageal cancer belongs to the cancer types with the highest risk for weight loss and malnutrition, Malnutrition is defined as a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome. In cancer patients malnutrition is due to cancer cachexia, which can be defined as a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment [10].

Before esophageal cancer surgery, this patient had 3 points of NRS2002 (nutritional screening risk), nutritional risk, "drinking water test" grade 3, mild dysphagia, and required nutritional support treatment. carrying out nutrition education on patients, guiding patients to eat semi-liquid or liquid diet, avoiding rough and irritating food, eating more fresh vegetables and fruits, taking enough fish, poultry, eggs, milk, beans and the like, Oral or nasal feeding ONS (oral nutrition supplement): 400g of enteral nutrition powder per day; Intravenous infusion of glucose, fat emulsion, amino acids and other nutrients. Patients are encouraged to do training such as climbing stairs to support muscle mass, body function and metabolic patterns [10]. Patients with postoperative NRS2002 score of parenteral nutrition or nasal feeding should be combined with ONS, adopt the principle of step by step according to the patient's tolerance, a small amount of multi-meal, select soft, moderate temperature, easy to digest food.

(2) Prevention of infection: Because esophagus cancer radical operation trauma, patients fear pain dare not expel sputum, and oral fasting is very easy to breed bacteria, so it is easy to appear in perioperative period wound infection and so on.

(a) Preoperative respiratory training should be given to patients: such as lip retraction breathing and abdominal breathing training, teaching patients effective coughing and coughing methods. No smoking, no alcohol, long-term smokers before surgery to give aerosol inhalation to promote the dilution and discharge of sputum. The patient was instructed to clean the body before surgery. Patients with oral diseases should be actively treated, patients should be instructed to maintain oral cleanliness, after three meals brushing teeth or chlorhexidine gargle, pre-operation teeth cleaning conditions.

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(b) The vital signs, especially the changes of body temperature, should be closely observed after the operation, and all kinds of laboratory tests should be done regularly. Assist the patient to take half lying position after anesthesia, regularly assist the patient to turn over and knock back, guide the patient to breathe deeply and cough effectively, and guide the patient to press the neck and chest wounds with both hands when coughing, which is beneficial to the discharge of the patient's sputum. At the same time, the patient should avoid repeated severe coughing so as not to affect the healing of the anastomosis. After the operation, the chest tube, neck drainage tube and gastric tube are regularly squeezed to maintain negative pressure, and the anti-reflux drainage bottle is regularly replaced to keep the wound clean and dry, and the wound dressing is promptly replaced when there is seepage. Early postoperative use of antibiotics intravenous drip, according to the sputum culture results timely replacement of antibiotics. Keep the ward environment clean and ventilate for half an hour in the morning and evening to assist patients to do basic nursing. When the patient is assessed to be able to eat, instruct the patient to chew the method 50 times and chew the food sufficiently before being swallowed.

(3) Atomized inhalation: Carotid arteries are very sensitive to changes in blood pressure [9]. Respiratory secretions can stimulate the throat to cause a patient to cough violently, leading to changes in blood pressure, humidification of the airway and aerosol inhalation help to dilute sputum, relieve symptoms of a patient's violent cough, and guide the patient to press a neck wound when coughing, Avoid increased anastomotic tension.

(4) Observation and nursing of cervical anastomotic fistula: Early anastomotic fistula occurs within 5 days after operation, the symptoms of the whole body are not obvious, palpation can find gas and liquid in neck incision; Mid-stage anastomotic fistula occurred in 6-14 days and was characterized by neck swelling and hot pain, palpation of subcutaneous emphysema and secretion of acid-odorous pus from neck incision; late anastomotic fistula occurred in more than 14 days and was characterized by systemic poisoning and increased pus. Nursing staff should pay attention to observation. The skin flap observation chart should be used to record the color, capillary filling degree and skin temperature in detail. If local skin is obviously white, swollen and skin temperature rise, patients feel local tension [9]. Report to the doctor as early as possible and improve the relevant examination so as to detect anastomotic fistula as early as possible. The patient has a mid-stage anastomotic fistula on the 8th day after operation. Diet should be immediately banned, neck incision is open and drained, effective gastrointestinal decompression is maintained, and gastric fluid gas is adequately drained, reducing the tension of anastomotic mouth and promoting the healing of the anastomotic mouth; Use high dose antibiotics to control infection according to drug sensitivity results; give high nutritional support to the veins or jejunum according to doctor's advice to enhance resistance and promote fistula healing; give systemic support treatment such as blood transfusion and transfusion according to doctor's advice; Strengthen the observation of vital signs and draining fluid traits; listen carefully to the patient's complaints and make psychological comfort; assist the patient to do basic nursing such as oral and perineal care; keep the ward quiet and proper temperature and humidity [11].

(5) Sufficient drainage of anastomosis: neck anastomosis close to the surface skin, easier drainage than thoracic fistula, anastomosis local inflammatory exudation more, so it is necessary to give local adequate drainage after neck surgery. After the anastomosis between the stomach and the esophagus, the gastric tube and the feeding tube are retained. The stump of the stomach wall is closed. a rubber strip is used for drainage at the neck, the rubber strip is removed and replaced with a gauze strip after 2 to 3 days, the neck is provided with 1cm open drainage for 2 to 3 days under the condition of ensuring smooth drainage at the neck, and the gauze strip is removed after the neck incision is completely cleaned, The neck incision was given about 2 days of healing time. Helps reduce the occurrence of neck anastomotic fistula and infection [12].

(6) Patients have few signs before their carotid arteries are about to rupture, including severe pain behind the sternum or in the upper abdomen, pulsating wounds, distended arteries, occasional small "harbingers" bleeding, the need for nurses to focus on high - risk patients, and their warning of bleeding signals [8]. If the doctor discovers the carotid artery is exposed when changing dressings, the arteries can be ligated before bleeding to prevent the occurrence of major bleeding.

(7) Equipped with a carotid artery rupture emergency treatment box, (Contains respiratory balloon, wound dressing, goggles, face screen, negative pressure device, oxygen inhalation device, air cut bag, with air bag catheter, intubation tube core, physiological saline, syringe, gloves, sedative drugs, local anesthesia drugs, gloves, etc.) [9], Periodically check the service life of the equipment, replace the equipment and stock if necessary, the ward should have the emergency plan of carotid rupture and drill smoothly.

5. Summary

Effective preventive observation is of great significance

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for early diagnosis of anastomotic fistula. In this case, due to preoperative radiotherapy and chemotherapy, malnutrition, neck anastomotic fistula after operation, pus infiltration and erosion of common carotid artery for a long time leading to massive hemorrhage, therefore, for esophageal cancer surgery patients, nutrition should be strengthened before operation to control infection, Strengthen basic nursing, pipeline nursing and early nutrition support after operation, discover anastomotic fistula in time and take care of it, pay attention to the precursors before bleeding, discover early and deal with it as soon as possible, and actively prepare for rescue. Familiarize and rehearse the emergency plan of carotid artery hemorrhage in advance, cooperate with the doctor actively, need the cooperation of multiple departments when rescuing the hemorrhage patient, should emphasize the team spirit between departments to make the patient recover early.

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ARTICLE

CDC20, TOP2A and NEK2 Expression in Esophageal Squamous Cell Carcinoma and Its Clinical Significance

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ABSTRACT

Objective: to study the expression and clinical significance CDC20, TOP2A, NEK2 esophageal squamous cell carcinoma. Methods: To select 70 patients with esophageal squamous cell carcinoma, Between August 2018 - August 2020, All intraoperative pathological specimens, A group -35 cases), Cancer tissue, B group, adjacent tissues), two groups of CDC20, TOP2A, NEK 2 expression were detected and analyzed by immunohistochemistry and semi-quantitative reverse transcription polymerase chain reaction -RT-PcR) assay.Results: the values of CDC20, TOP2A, NEK2 expression level in A group were significantly higher than those in B group -P<0.05). The expression level CDC20, TOP2A, NEK2 esophageal squamous cell carcinoma was positively correlated with TNM stage and lymphatic metastasis, and negatively correlated with tumor differentiation. Conclusion: CDC20, TOP2A, NEK2 high expression level directly affects the metastasis, recurrence and prognosis of esophageal squamous cell carcinoma. The combination of three indexes can accurately evaluate the pathological status of patients with esophageal squamous cell carcinoma and help to judge the prognosis of patients accurately.

1. Introduction

Esophageal squamous cell carcinoma is a malignant tumor of digestive tract with high clinical incidence. According to the World Health Organization report, esophageal squamous cell carcinoma in the world ranked eighth, mortality ranked sixth. In our country, phase the five-year survival rate in patients with esophageal squamous cell carcinoma is between 15% and 25%, according to the study [1]. With the development of modern medical research on the biological mechanism and molecular mechanism of esophageal squamous cell carcinoma, the gene and protein development mechanism related to this disease has made great progress. Related studies have confirmed that TOPA2 expression directly affects tumor cell apoptosis, while cell division cyclin 20-CDC20) has a positive effect on tumor cell infiltration. Mitotic regulatory kinase 2-NEK2) was significantly abnormal in pathological tissues of end-stage tumor patients. Expression and clinical significance CDC20, TOP2A, NEK2 esophageal squamous cell carcinoma were discussed.

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2. Information and Methodology

2.1 General Information

The patients with esophageal squamous cell carcinoma were selected from 70 cases of esophageal squamous cell carcinoma. The interval was August 2018 - August 2020. All the samples were collected by intraoperative pathology, A group -35 cases, cancer tissue), B group -35 cases, adjacent tissue).

Among them, Male patients 56, female patients 24; Between 45 -72, Mean -62.15+2.25) years; TNM staging:12 cases in phase I, A total of 33 cases in phase II, A total of 23 cases in phase III, Phase IV totalled 12 cases; Tumor differentiation: a total of 42 cases of middle and high differentiation, A total of 38 cases of low differentiation; Lymphatic metastasis: a total of 33 cases, There were 47 cases without lymphatic metastasis. Inclusion criteria:1 all included patients did not carry out radiotherapy and chemotherapy before operation; -2) indication of surgical resection; 3. Complete case examination data; Know the contents of the test and sign the agreement. Exclusion criteria:1 with severe complications; Preoperative radiotherapy and chemotherapy; 3 Poor coordination. Above data is balanced -P>0.05).

2.2 Method

Routine formaldehyde -10% concentration) was used to fix all samples. The fixation time was controlled between 4 -6 h. Gradient dehydration, tissue wax immersion, paraffin embedding, sectioning, immunohistochemical S-P method were used to observe and evaluate the expression gray value of CDC20, TOP2A, NEK2 in esophageal squamous cell carcinoma. Results: two experienced pathologists were arranged to observe tumor cells, nuclei or cytoplasm by high magnification -×400) under the condition of double blind method. Once yellow or brown granules were found, positive cells could be determined. Select 5 visual fields for each specimen, And 100 tumor cell counts per field of vision, Total 500, The statistical ratio of positive cells was calculated accurately. Positive criteria: positive cell rate of 10% and above; Negative criteria: positive cell rate less than 10%. Semi-quantitative reverse transcription polymerase chain reaction -RT-PCR) to accurately detect CDc20, TOP2A, NEK2 expression factors in the pathological tissue of patients, The extraction and DEPC preparation of gene RNA according to the standard protocol of the TrizolRNA kit, MRNA integrity was identified by agarose gel electrophoresis. That is, the practical ABl7500 real-time quantitative PCR instrument, Can achieve the purpose of specimen gene amplification, After uVIpro ultraviolet gel imaging and analysis system observation, scanning, photography and other series of operations, The CDC20, TOP2A, NEK2 and β-actin expression intensity in the picture were observed and analyzed.

2.3 Statistical Analysis

The experimental data are processed in parallel SPSS19.0 new model building, in which the qualitative data are expressed as percentage -%) and the test χ is used^{2}The quantitative data showed that the results were statistically significant P<0.05.

3. Results

3.1 CDC20, TOP2A, NEK2 Expressional Characteristics

S-P results showed that the cancer cells were nest-like distribution, accompanied by irregular cell series, abnormal cells, nuclear mitosis, and obvious positive particles in the cytoplasm.

3.2 Analysis of CDC20, TOP2A, NEK2 Expression in Different Esophageal Tissue Samples

The values of CDC20, TOP2A, NEK2 expression level in A group were significantly higher than those in B group -P<0.05) (See Table 1).

Table 1. Analysis of CDC20, TOP2A, NEK2 expression in different esophageal tissue samples -±s)

Group	CDC20		TOP2A		NEK2	
	mRNA Relative Expression Coefficient	The gray level of protein expression	mRNA Relative Expression Coefficient	The gray level of protein expression	mRNA Relative Expression Coefficient	The gray level of protein expression
A group	1.259±0.246	15.259±4.258	0.668±0.118	54.892±1.976	0.856±0.176	1.235±0.068
B group	0.967±0.168	10.072±4.224	0.516±0.084	42.772±1.617	0.702±0.151	0.865±0.032
t	5.799	5.116	6.208	28.083	3.929	29.127
p	0.000	0.000	0.000	0.000	0.000	0.000

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Table 2. CDC20, TOP2A, NEK2 Expression and clinicopathological features and correlation analysis

Clinical data	Number of cases	CDC20 positive	x^2	P	TOP2A	x^2	P	NEK2	x^2	P
TNM staging			8.903	0.003		6.612	0.010		8.762	0.002
Ⅰ	12	4 (33.33)			3 (25.00)			2 (16.67)		
Ⅱ	33	20 (60.61)			19 (57.58)			17 (51.52)		
Ⅲ	23	18 (78.26)			18 (78.26)			20 (86.96)		
Ⅳ	12	11 (91.67)			10 (83.33)			12 (100.00)		
Tumor differentiation			5.038	0.025		6,737	0.009		5.402	0.020
Medium High Differentiation	42	28 (66.67)			25 (59.52)			29 (69.05)		
Low differentiation	38	32 (84.21)			30 (78.95)			20 (52.63)		
lymphatic metastasis			8.202	0.004		4.369	0.037		4.716	0.029
Yes	33	26 (78.79)			24 (72.73)			25 (75.76)		
No	47	27 (57.44)			27 (57.44)			28 (49.12)		

3.3 CDC20, TOP2A, NEK2 Expression and Clinicopathological Features and Correlation Analysis

The expression level CDC20, TOP2A, NEK2 esophageal squamous cell carcinoma was positively correlated with TNM stage and lymphatic metastasis, and negatively correlated with tumor differentiation (See Table 2).

4. Discussion

CDC20 cell cyclin plays a key role in the normal mitosis of cells, mainly in the -G stage of cell mitosis$_2$The effective regulation of chromosome DNA division and replication in M cells and the active promotion of positive regulators in late complex / periodic APC/C. Studies have confirmed that the occurrence of CDC20 abnormal expression is likely to cause mitosis errors, and will lead to the wrong expression of some cancer genes and tumor suppressor gene mutations or even disappear. Abnormal CDC20 expression can create better conditions for the proliferation and self-repair of cancer cells, leading to the risk of uncontrolled tumor inhibition in cancer patients greatly increased [2]. In addition, CDC20 can slow down the apoptosis rate of tumor cells and play an important role in tumor progression. can be seen that CDC20 as a new target for tumor therapy is highly feasible. According to relevant studies, esophageal squamous cell carcinoma is closely related to molecular biological factors, including activation / inactivation of proto-cancer / tumor suppressor gene, repair of regulatory DNA and dysfunction of regulatory proteins that maintain gene stability. TOP2A is an important regulatory enzyme in the nucleus, second only to histone protease. Its mechanism is to control and change the topological state of DNA transcriptional network and the transcription of DNA. It has good effect on the function regulation of chromosome condensation and chromatid separation [3]. Studies have shown that TOPA2 can promote the formation of TOP-DNA-AMPPNP complexes and participate effectively in cell mitosis by shearing DNA,. NEIK2 can establish bipolar spindle quickly by regulating the central body to copy, separate and mature correctly. At present, it has been proved that NEK2 expression is high in many tumors and malignant glioma tissues, and with the progression of malignant tissues, the expression level of malignant tissues increases significantly [4]. Abnormal NEK2 expression is highly likely to cause abnormal changes in centrosome structure, which in turn leads to functional defects, which will lead to the overall stability of infected genes, induce malignant transformation of cells and participate in tumor metastasis and infiltration.

The results showed that CDC20, TOP2A, NEK2 and other expression factors in esophageal squamous cell carcinoma showed a high level, which showed an increasing trend compared with adjacent tissues, and the data between groups were significantly different, and there was a positive correlation with TNM stage, tumor differentiation, lymphatic metastasis and other related factors. CDC20, TOP2A, NEK2 directly affects the pathological progression and metastasis of esophageal squamous cell carcinoma. Therefore, the abnormal expression of CDC20, TOP2A, NEK2 is beneficial to the prediction and evaluation of invasion, metastasis and recurrence of esophageal squamous cell carcinoma, and with the aggravation of TNM stage, the expression of its indexes is obviously on the rise. By CDC20, TOP2A,

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NEK2 joint examination, it can provide reliable reference for the evaluation of the deterioration and development mechanism, stage and differentiation degree of esophageal squamous cell carcinoma, and improve the clinical diagnosis and treatment effect of esophageal squamous cell carcinoma. Combined CDC20, TOP2A, NEK2 therapy is of great significance for the evaluation of pathological status and prognosis of esophageal squamous cell carcinoma.

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1. Main Manuscript
2. Reference List
3. Supplementary Data/Information

Supplementary figures, small tables, text etc.

As supplementary data/information is not copyedited/proofread, kindly ensure that the section is free from errors, and is presented clearly.

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A general introduction to the research topic of the paper should be provided, along with a brief summary of its main results and implications. Kindly ensure the abstract is self-contained and remains readable to a wider audience. The abstract should also be kept to a maximum of 200 words.

Authors should also include 5-8 keywords after the abstract, separated by a semi-colon, avoiding the words already used in the title of the article.

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Ⅳ. Section Headings

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The introduction should highlight the significance of the research conducted, in particular, in relation to current state of research in the field. A clear research objective should be conveyed within a single sentence.

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In this section, the methods used to obtain the results in the paper should be clearly elucidated. This allows readers to be able to replicate the study in the future. Authors should ensure that any references made to other research or experiments should be clearly cited.

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Ⅸ. Conclusion

This section offers closure for the paper. An effective conclusion will need to sum up the principal findings of the papers, and its implications for further research.

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Ⅺ. Glossary of Publication Type

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Conflicts of interest, acknowledgements, and publication ethics should also be declared in the final version of the manuscript. Instructions have been provided as its counterpart under Cover Letter.

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