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Effect of intraperitoneal hyperthermic perfusion chemotherapy after laparoscopic surgery for colorectal cancer and the changes in the HMGB1/RAGE axis level

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Abstract: Objective To investigate the efficacy of hyperthermic intraperitoneal chemotherapy (HIPEC) after laparoscopic surgery for colorectal cancer and the changes in the high mobility group box 1 (HMGB1) /receptor for advanced glycation end products (RAGE) axis, providing a reference for clinical treatment. **Methods** A total of 152 colorectal cancer patients who underwent laparoscopic surgery at Taiyuan Central Hospital from May 2021 to March 2024 were selected and randomly divided into an observation group (n=76) and a control group (n=76) using a random number table. The control group received XELOX chemotherapy, while the observation group received additional HIPEC. The general surgical conditions, recovery conditions, efficacy, tumor markers [vascular endothelial growth factor (VEGF), matrix metalloproteinase-9 (MMP9), carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199)], immune function ($CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$), HMGB1/RAGE axis, adverse reactions, and recurrence/metastasis during follow-up were compared between the two groups. **Results** There were no significant differences in incision length, operation time, intraoperative blood loss, or postoperative exhaust time between the two groups ($P>0.05$). The total effective rate in the observation group was higher than that in the control group (88.16% vs 75.00%, $P<0.05$). After 1 and 3 cycles of chemotherapy, serum levels of CEA, VEGF, MMP9, and CA199 in the observation group were lower than those in the control group ($P<0.05$). After 1 and 3 cycles of chemotherapy, $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ levels in the observation group were higher than those in the control group, while CD8 + levels were lower ($P<0.05$). Serum HMGB1 and RAGE levels in the observation group were lower than those in the control group after 1 and 3 cycles of chemotherapy ($P<0.05$). There was no significant difference in adverse reactions between the two groups ($P>0.05$). After 6 months of follow-up, the disease-free survival rate in the observation group was higher than that in the control group (93.42% vs 82.89%, $\chi^2=4.033$, $P<0.05$). **Conclusion** HIPEC after laparoscopic surgery for colorectal cancer demonstrates good efficacy, improves immune function, and may be associated with the HMGB1/RAGE axis, without significantly increasing adverse reactions, indicating a certain level of safety.

Keywords: Colorectal cancer; Hyperthermic intraperitoneal chemotherapy; Laparoscopic surgery; High mobility group box 1; Receptor for advanced glycation end products; Safety

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Colorectal cancer is a common malignant tumor of the digestive system. Its onset is insidious, and most patients are diagnosed in advanced stages, where surgery alone is insufficient for a cure. Laparoscopic surgery is a commonly used treatment for colorectal cancer and has a relatively high safety profile. However, there remains a risk of recurrence and metastasis post-surgery, making adjuvant chemotherapy particularly important [1-2]. The XELOX regimen is a commonly used chemotherapy regimen for colorectal cancer, which kills cancer cells through chemotherapy drugs and helps suppress cancer cell proliferation [3]. During XELOX systemic intravenous chemotherapy, the drug concentration is insufficient to completely eradicate intra-abdominal cancer cells. While increasing the drug dose can improve chemotherapy efficacy to some extent, it also increases the toxic side effects [4]. In recent years, hyperthermic intra-peritoneal chemotherapy (HIPEC) has gradually been used as adjuvant therapy after colorectal cancer surgery. By injecting chemotherapy drugs into the abdominal cavity, it can maintain a high concentration of the drugs locally for an extended period, directly eliminating shed cancer cells or microscopic metastatic lesions [5-6]. Currently, the critical role of inflammation in the carcinogenesis process of body cells is recognized, but the exact mechanism of how inflammatory pathways contribute to carcinogenesis is still unclear. High mobility group box 1 (HMGB1) is an advanced inflammatory factor that is widely present in the nuclei of eukaryotic cells. It regulates gene transcription and, when released extracellularly, mediates inflammatory responses [7]. The receptor for advanced glycation end products (RAGE) is a single-pass transmembrane protein and a multi-ligand transmembrane signaling receptor. When HMGB1 binds

to RAGE, it can activate downstream inflammatory signaling pathways [8-9]. Understanding the role of the HMGB1/RAGE axis in colorectal cancer may provide new insights for clinical targeted therapies. Therefore, this study aims to explore the effects and safety of HIPEC combined with laparoscopic surgery in regulating the HMGB1/RAGE axis in the treatment of colorectal cancer. The report is as follows.

1. Materials and Methods

1.1 General Information

This prospective study selected 152 patients with colorectal cancer who underwent laparoscopic surgery at Taiyuan City Central Hospital from May 2021 to March 2024. They were randomly divided into observation and control groups, with 76 patients in each group, using the random number table method. The study was approved by the hospital's ethics committee (Ethics approval number: 20200119), and informed consent was obtained from the patients and their families.

Inclusion criteria: Diagnosed according to the " Chinese protocol of diagnosis and treatment of colorectal cancer(2020 edition)" [10]; confirmed by pathological examination; underwent laparoscopic surgery; no distant metastasis on preoperative examination; Karnofsky score ⩾ 70; TNM stage III or PCI score <17 for stage IV colorectal cancer; met the indications for laparoscopic surgery and HIPEC; no history of radiotherapy or chemotherapy; no contraindications for HIPEC or systemic intravenous chemotherapy.

Exclusion criteria: Presence of abdominal infection; estimated survival time <6 months; history of complicated abdominal surgery; significant liver, heart, or kidney dysfunction; presence of bowel obstruction or perforation requiring emergency surgery; concurrent other malignancies; pregnant or breastfeeding women; mental disorders preventing normal communication.

In the control group, there were 46 male and 30 female patients, aged 45-64 years (53.82±4.39), with a BMI of 23-26 kg/m² (23.61±0.92). The group included 47 cases of colon cancer and 29 cases of rectal cancer. The tumor diameter ranged from 2.5 to 4.5 cm (3.74±0.28). Pathological types were adenocarcinoma in 43 cases, undifferentiated carcinoma in 19 cases, and mucinous carcinoma in 14 cases. TNM stages were 49 cases of stage III and 27 cases of stage IVa. The PCI score ranged from 11 to 16 (13.86±0.72). The American Society of Anesthesiologists (ASA) classification included 35 cases of grade I, 32 cases of grade II, and 9 cases of grade III.

In the observation group, there were 43 male and 33 female patients, aged 43-66 years (54.47±5.23), with a BMI of 21-27 kg/m² (23.83±1.05). The group included 42 cases of colon cancer and 34 cases of rectal cancer. Tumor diameter ranged from 3 to 5 cm (3.80±0.31). Pathological types were adenocarcinoma in 41 cases, undifferentiated carcinoma in 17 cases, and mucinous carcinoma in 18 cases. TNM stages included 45 cases of stage III and 31 cases of stage IVa. PCI score ranged from 12 to 16 (14.07±0.79). ASA classification included 32 cases of grade I, 34 cases of grade II, and 10 cases of grade III. No statistically significant differences in baseline data were found between the two groups (P > 0.05), ensuring comparability.

1.2 Methods

Both groups underwent laparoscopic radical surgery: General anesthesia with intravenous inhalation was applied, and a 1 cm incision was made below the umbilicus to establish pneumoperitoneum. A laparoscope was inserted, and an ultrasonic scalpel was used to separate the abdominal wall. The inferior mesenteric artery was ligated, and lymph nodes were dissected. The peritoneum was opened, the tumor and affected bowel segments were excised, and the bowel ends were sutured. Gastrointestinal reconstruction was performed using a gastrointestinal anastomosis device. Blood flow was confirmed, and the abdominal cavity was irrigated. Drainage tubes were placed based on the situation, and the abdomen was closed. Postoperatively, a venous patient-controlled analgesia pump was used.

1.2.1 Control Group

The control group received XELOX regimen chemotherapy after laparoscopic radical surgery. On day 1 of chemotherapy, oxaliplatin (Hayao Group Bioengineering Co., Ltd., approval number: H20133094) 100 mg/m² was intravenously infused over 3 hours. On days 1-14 of chemotherapy, capecitabine (Nanjing Yuke Pharmaceutical Co., Ltd., approval number: H20223015) 850-1000 mg/m² was administered orally twice a day. After 3 cycles, efficacy was assessed.

1.2.2 Observation Group

In addition to the treatment in the control group, the observation group received HIPEC. Two infusion drainage tubes were placed in both the upper and lower abdomen. HIPEC treatment was initiated on the second postoperative day using a body cavity hyperthermic perfusion machine. The perfusion fluid consisted of 2 g of 5-fluorouracil (Liaoning Xinguo Pharmaceutical Co., Ltd., approval number: H21024236) and 4,000 mL of 0.9% saline. The perfusion temperature was maintained at 43°C, with a flow rate of 100-800 mL/min. Drainage tubes were retained, and the treatment was repeated every two days for a total of 3 treatments.

1.2.3 Follow-up

Post-treatment follow-up was conducted via telephone and outpatient visits for 6 months to assess recurrence, metastasis, and disease-free survival.

1.3 Observation Indicators

(1) Comparison of surgical conditions between the two groups.

(2) Comparison of efficacy between the two groups.

After completing 3 cycles of chemotherapy, efficacy was evaluated as follows [11]. Complete response: Complete disappearance of the lesion, maintained for ≥4 weeks. Partial response: The volume of the lesion shrank by >30% compared to pre-treatment, maintained for ≥4 weeks. Stable disease: The lesion size decreased by <30% or increased by <20%. Progressive disease: The lesion size increased by ≥20% or new lesions appeared. The total effective rate = (complete response + partial response) / total cases × 100%.

(3) Comparison of tumor markers before surgery, and after 1 and 3 cycles of chemotherapy. Blood (5 mL) was drawn from each group, and after centrifuging at 3500 r/m for 12 minutes, serum levels of carbohydrate antigen 199 (CA199), carcinoembryonic antigen (CEA), matrix metalloproteinase 9 (MMP9), and vascular endothelial growth factor (VEGF) were measured using enzyme-linked immunosorbent assay (ELISA).

(4) Comparison of immune function before surgery, and after 1 and 3 cycles of chemotherapy. T-lymphocyte subsets ($CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$) were detected by flow cytometry (Beckman Coulter FC-500).

(5) Comparison of the HMGB1/RAGE axis before surgery, and after 1 and 3 cycles of chemotherapy. Serum HMGB1 and RAGE levels were detected by ELISA.

(6) Comparison of toxic and side effects between the two groups. Toxicity was graded according to the WHO standard for common chemotherapy side effects, ranging from grade 0 to IV. The higher the grade, the greater the toxicity.

(7) Comparison of recurrence, metastasis, and disease-free survival between the two groups.

1.4 Statistical Methods

Data were analyzed using SPSS 27.0 software. Normally distributed continuous variables were presented as means ± standard deviations ($\bar{x}\pm s$). Group comparisons were made using independent sample *t*-tests. Repeated measures analysis of variance was used for multi-time point comparisons. When no interaction effect was found between time and treatment factors, main effect tests were performed. If an interaction effect was present, within-group effects and between-group effects were analyzed using one-way repeated measures ANOVA and multivariate analysis of variance. Bonferroni's correction was applied for pairwise comparisons, with a significance level of $\alpha = 0.05$. Count data were presented as n (%), and comparisons were made using the chi-square test.

2. Results

2.1 Comparison of surgical conditions between the two groups

There were no statistically significant differences in the surgical time, incision length, intraoperative blood loss, and postoperative flatus time between the two groups ($P > 0.05$). See Table 1.

2.2 Comparison of therapeutic efficacy between the two groups

The overall efficacy rate in the observation group was higher than that in the control group, and the difference was statistically significant ($P < 0.05$). See Table 2.

Tab.1 Comparison of general surgical conditions and recovery between two groups (n=76, $\bar{x}\pm s$)

Group	Operation Time (min)	Incision Length (cm)	Intraoperative Blood Loss (mL)	Postoperative Exhaust Time (d)
Observation Group	140.10±35.38	4.62±1.13	103.24±24.87	3.10±0.91
Control Group	137.24±36.24	4.70±1.50	106.86±25.12	3.23±1.04
t value	0.492	0.371	0.893	0.820
P value	0.623	0.711	0.373	0.413

Tab.2 Comparison of efficacy between two groups [case(%)]

Group	Complete response	Partial response	Stable disease	Progressive disease	total effective
Observation Group	24	43	9	0	67 (88.16)
Control Group	17	40	19	0	57 (75.00)
χ^2 value					4.378
P value					0.036

2.3 Comparison of tumor markers between the two groups

The time effect, group effect, and interaction effect for serum CEA, VEGF, MMP9, and CA199 at different time points showed statistical significance ($P < 0.05$). The time effect and group effect were tested separately. Bonferroni's method was used to adjust the test level to $\alpha = 0.05$ ($\alpha' = 0.02$). The comparison of serum CEA, VEGF, MMP9, and CA199 at different time points between the two groups showed statistically significant differences ($P < 0.02$). Multivariate analysis of variance showed that after one cycle of chemotherapy and after three cycles of chemotherapy, the levels of serum CEA, VEGF, MMP9, and CA199 in the observation group were lower than those in the control group ($P < 0.02$). See Table 3.

2.4 Comparison of immune function between the two groups

The time effect, group effect, and interaction effect for $CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ at different time points were statistically significant ($P < 0.05$). The time effect and group effect were tested separately ($\alpha' = 0.02$). The comparison of $CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ between the two groups at different time points showed statistically significant differences ($P < 0.02$). The results of multivariate analysis of variance showed that after one cycle of chemotherapy and after three cycles of chemotherapy, the levels of $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ in the observation group were higher than those in the control group, while the level of $CD8^+$ was lower in the

observation group ($P < 0.02$). See Table 4.

2.5 Comparison of HMGB1/RAGE axis between the two groups

The time effect, group effect, and interaction effect for serum HMGB1 and RAGE at different time points were statistically significant ($P < 0.05$). The time effect and group effect were tested separately ($\alpha' = 0.02$). The comparison of serum HMGB1 and RAGE at different time points between the two groups showed statistically significant differences ($P < 0.02$). The results of multivariate analysis of variance showed that after one cycle of chemotherapy and after three cycles of chemotherapy, the levels of serum HMGB1 and RAGE in the observation group were lower than those in the control group ($P < 0.02$). See Table 5.

2.6 Comparison of adverse effects between the two groups

There were no statistically significant differences between the two groups in terms of nausea and vomiting, liver function damage, and leukopenia ($P > 0.05$). See Table 6.

2.7 Comparison of recurrence, metastasis, and disease-free survival between the two groups

After 6 months of follow-up, there were 5 cases of recurrence and metastasis in the observation group, and 71 patients with disease-free survival. In the control group, there were 13 cases of recurrence and metastasis, and 63 patients with disease-free survival. The disease-free survival rate in the observation group was higher than that in the control group (93.42% vs 82.89%, $\chi^2 = 4.033$, $P < 0.05$).

Tab.3 Comparison of tumour markers between two groups (n=76, $\bar{x}\pm s$)

Indicator	Group	Preoperative	After 1 Chemotherapy Cycle	After 3 Chemotherapy Cycles
CEA (pg/mL)	Observation group	28.34±5.92	17.52±3.82	4.46±1.38
	Control group	28.78±5.31	20.04±3.67	5.33±1.62
	F value	F_{group}=11.624, F_{time}=19.622, $F_{interaction}$=25.495		
	P value	$P_{group}<0.001$, $P_{time}<0.001$, $P_{interaction}<0.001$		
VEGF (ng/L)	Observation group	648.81±130.83	497.51±96.54	403.10±81.45
	Control group	660.23±142.79	542.38±112.60	449.63±85.29
	F value	F_{group}=19.375, F_{time}=26.388, $F_{interaction}$=40.152		
	P value	$P_{group}<0.001$, $P_{time}<0.001$, $P_{interaction}<0.001$		
MMP9 (ng/L)	Observation group	583.72±120.63	367.81±93.55	294.23±73.84
	Control group	566.48±134.65	414.57±100.83	341.05±83.51
	F value	F_{group}=15.030, F_{time}=23.659, $F_{interaction}$=34.572		
	P value	$P_{group}<0.001$, $P_{time}<0.001$, $P_{interaction}<0.001$		
CA199 (pg/mL)	Observation group	26.88±3.96	20.19±3.10	18.81±2.72
	Control group	26.39±4.02	23.70±3.68	21.57±3.11
	F value	F_{group}=14.243, F_{time}=21.165, $F_{interaction}$=28.694		
	P value	$P_{group}<0.001$, $P_{time}<0.001$, $P_{interaction}<0.001$		

Tab.4 Comparison of Immune Function between two groups (n=76, $\bar{x}\pm s$)

Indicator	Group	Preoperative	After 1 Chemotherapy Cycle	After 3 Chemotherapy Cycles
$CD3^+$ (%)	Observation group	50.17±4.12	61.54±5.49	71.23±6.03
	Control group	48.96±5.37	56.31±5.53	65.30±5.22
	F value	F_{group}=12.254, F_{time}=16.257, $F_{interaction}$=25.830		
	P value	$P_{group}<0.001$, $P_{time}<0.001$, $P_{interaction}<0.001$		
$CD4^+$ (%)	Observation group	31.07±3.99	38.64±4.31	43.55±4.72
	Control group	32.35±4.12	35.37±4.02	37.51±3.97
	F value	F_{group}=11.538, F_{time}=18.433, $F_{interaction}$=28.017		
	P value	$P_{group}<0.001$, $P_{time}<0.001$, $P_{interaction}<0.001$		
$CD8^+$ (%)	Observation group	30.41±3.34	23.64±2.54	21.03±2.42
	Control group	30.36±3.62	26.87±2.69	24.96±2.56
	F value	F_{group}=14.109, F_{time}=23.064, $F_{interaction}$=37.455		
	P value	$P_{group}<0.001$, $P_{time}<0.001$, $P_{interaction}<0.001$		
$CD4^+/CD8^+$	Observation group	1.02±0.31	1.63±0.50	2.07±0.62
	Control group	1.07±0.33	1.32±0.36	1.50±0.38
	F value	F_{group}=9.561, F_{time}=14.586, $F_{interaction}$=24.348		
	P value	$P_{group}<0.001$, $P_{time}<0.001$, $P_{interaction}<0.001$		

Tab.5 Comparison of HMGB1/RAGE axis between two groups (n=76, $\bar{x}\pm s$)

Indicator	Group	Preoperative	After 1 Chemotherapy Cycle	After 3 Chemotherapy Cycles
HMGB1 (ng/mL)	Observation group	3.19±0.95	1.27±0.34	0.86±0.24
	Control group	2.96±0.83	1.54±0.54	1.29±0.37
	F value	F_{group}=10.823, F_{time}=13.625, $F_{interaction}$=21.582		
	P value	$P_{group}<0.001$, $P_{time}<0.001$, $P_{interaction}<0.001$		
RAGE (pg/mL)	Observation group	318.52±49.33	214.28±42.05	156.30±36.59
	Control group	309.11±47.29	257.43±47.81	188.16±41.57
	F value	F_{group}=17.951, F_{time}=22.483, $F_{interaction}$=35.038		
	P value	$P_{group}<0.001$, $P_{time}<0.001$, $P_{interaction}<0.001$		

Tab.6 Comparison of toxic and side effects between two groups (case)

Group	Nausea and Vomiting		Liver Function Damage		Leukopenia	
	I-II	III-IV	I-II	III-IV	I-II	III-IV
Observation group	19	11	11	5	14	5
Control group	16	14	10	3	9	3
χ^2 value	0.617		0.621		1.992	
P value	0.734		0.733		0.369	

3. Discussion

Colorectal cancer ranks third in incidence among malignant tumors in China, and its incidence is increasing yearly, with nearly 400,000 new cases each year. It has become one of the major social health problems in China [12-13].

HIPEC is a novel tumor adjunctive therapy that delivers chemotherapy drugs directly into the peritoneal cavity of colorectal cancer patients through an infusion drainage tube, with features of circulating perfusion and precise constant temperature [14-15]. This study shows

that after one and three cycles of chemotherapy, the levels of $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ in the observation group were higher than those in the control group, while CD8+, serum CEA, VEGF, MMP9, and CA199 levels were lower in the observation group. Compared to the control group, the observation group had fewer recurrences and metastases, and a higher proportion of patients achieved disease-free survival. These results suggest that HIPEC combined with laparoscopic surgery can better control the disease in colorectal cancer patients, improve immune function, and regulate serum tumor marker levels. The effects of HIPEC on colorectal cancer mainly include: it can effectively increase the local drug concentration, extend the contact time between tumor tissues and high-concentration drugs, accurately and efficiently eliminate residual tumor cells in the peritoneal cavity, and avoid drug accumulation in the bloodstream [16-17]. Additionally, the heat effect of HIPEC can directly affect the chromosomes of tumor cells, promote the release of lysozyme, enhance the cytolytic effect on tumor cells, reduce the levels of serum tumor markers, and improve disease control [18]. Moreover, chemotherapy drugs used in HIPEC can also reach the portal vein via the peritoneum, thereby increasing the drug concentration in the liver and controlling liver metastases from colorectal cancer [19]. After tumor surgery, colorectal cancer patients generally have low immune function due to the tumor itself and the surgical procedure. HIPEC accelerates blood flow and vasodilation through its thermal effect, which helps induce the body's anti-tumor immune response, improves immune function, and promotes tumor cell apoptosis, ultimately improving the prognosis of colorectal cancer treatment. The results of this study showed no statistically significant difference in adverse effects between the two groups. This may be because HIPEC is a local treatment method, and the peritoneal barrier function can slow down the diffusion and absorption of macromolecular drugs during HIPEC, maintaining a high drug concentration in the peritoneal cavity to effectively kill cancer cells. Furthermore, after chemotherapy drugs are metabolized in the liver and enter the peripheral circulation, the side effects of chemotherapy drugs are reduced [20].

Chronic inflammation is a key feature of tumors and promotes an immune-suppressive tumor microenvironment that facilitates tumor initiation and progression. The development of colorectal cancer is closely related to its inflammatory microenvironment. Studies have shown that the binding of HMGB1 and RAGE can participate in the proliferation and invasion of various tumor cells [21]. Research by Yang *et al.* [22] indicated that serum HMGB1 and RAGE in early cervical cancer patients were positively correlated with malignant biological factors of tumors, such as Caspase-3, bel-2, and MMP-1. Yi Zhenghong et al. [23] reported that overexpression of HMGB1 could reverse, to some extent, the inhibitory effect of Gynostemma saponin on the malignant biological behavior of osteosarcoma cells. The results of this study show that the overall efficacy rate of the observation group was higher than that of the control group, and the serum HMGB1 and RAGE levels in the observation group after one and three cycles of chemotherapy were lower than those in the control group. This indicates that the expression of HMGB1 and RAGE proteins is upregulated in colorectal cancer cells, and downregulating HMGB1 and RAGE expression may help improve the treatment efficacy for colorectal cancer. The mechanism of the HMGB1/RAGE axis likely involves inflammation, immune modulation, and regulation of chemotherapy sensitivity. Chronic inflammation in colorectal cancer patients can upregulate the expression of HMGB1 and RAGE proteins. The large release of HMGB1 and RAGE enhances local inflammatory responses, activates transcriptional co-activators downstream of the RAS signaling pathway, and stimulates tumor cell proliferation through the HMGB1-RAGE axis [24-25]. HIPEC combined with laparoscopic surgery may regulate the tumor microenvironment through the HMGB1-RAGE axis, activate the immune system, antagonize cell proliferation, and induce tumor cell apoptosis. In colorectal cancer patients after laparoscopic surgery, HIPEC delivers high concentrations of chemotherapy drugs directly to the residual tumor tissues, and its higher drug efficacy compared to systemic administration significantly enhances the tumor-killing effect [26-27]. Furthermore, the high temperature effect of HIPEC can enhance lysosomal activity in cancer cells, destroy their stability, reduce the residual tumor burden, and synergistically improve anti-tumor immunity. This may involve downregulating the expression of HMGB1 and RAGE, inhibiting tumor-related inflammatory responses, and improving treatment outcomes [28].

In conclusion, HIPEC combined with laparoscopic surgery can effectively improve the immune function of colorectal cancer patients, regulate tumor marker levels, potentially act through the HMGB1/RAGE axis, and enhance treatment outcomes with a certain degree of safety.

Conflict of interest None

Reference

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·论　著·

腹腔镜手术治疗结直肠癌后腹腔热灌注化疗的效果及HMGB1、RAGE水平变化

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摘要：目的　探讨腹腔镜手术治疗结直肠癌后腹腔热灌注化疗（HIPEC）的效果，以及高迁移率族蛋白1（HMGB1）和晚期糖基化终产物受体（RAGE）水平变化，为临床治疗提供参考。**方法**　选取2021年5月至2024年3月太原市中心医院收治的152例接受腹腔镜手术治疗的结直肠癌患者，按照随机数字表法分为观察组（n=76）和对照组（n=76），其中对照组给予XELOX方案化疗，观察组在此基础上给予HIPEC。比较两组手术一般情况及恢复情况、疗效、肿瘤标志物[血管内皮生长因子（VEGF）、基质金属蛋白酶9（MMP9）、癌胚抗原（CEA）、糖类抗原199（CA199）]、免疫功能（$CD3^+$、$CD4^+$、$CD8^+$、$CD4^+/CD8^+$）、HMGB1、RAGE、毒副反应及随访期间复发转移情况。**结果**　两组切口长度、手术时间、术中出血量、术后排气时间比较差异均无统计学意义（$P>0.05$）；观察组总有效率高于对照组（88.16% *vs* 75.00%，$P<0.05$）；观察组化疗1、3个周期后血清CEA、VEGF、MMP9、CA199水平均低于对照组（$P<0.02$）；观察组化疗1、3个周期后$CD3^+$、$CD4^+$、$CD4^+/CD8^+$水平均高于对照组，$CD8^+$水平低于对照组（$P<0.02$）；观察组化疗1、3个周期后血清HMGB1、RAGE均低于对照组（$P<0.02$）；两组毒副反应比较差异无统计学意义（$P>0.05$）；随访6个月，观察组无病生存比例高于对照组（93.42% *vs* 82.89%，$\chi^2=4.033$，$P<0.05$）。**结论**　结直肠癌腹腔镜手术治疗后行HIPEC有良好疗效，可改善患者免疫功能，其作用可能与HMGB1/RAGE轴有关，且未明显增加毒副反应，有一定安全性。

关键词：结直肠癌；腹腔热灌注化疗；腹腔镜手术；高迁移率族蛋白1；晚期糖基化终产物受体；安全性
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Effect of intraperitoneal hyperthermic perfusion chemotherapy after laparoscopic surgery for colorectal cancer and the changes in the HMGB1 and RAGE level

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Abstract: Objective　To investigate the efficacy of hyperthermic intraperitoneal chemotherapy (HIPEC) after laparoscopic surgery for colorectal cancer and the changes in the high mobility group box 1 (HMGB1) and receptor for advanced glycation end products (RAGE), providing a reference for clinical treatment. **Methods**　A total of 152 colorectal cancer patients who underwent laparoscopic surgery at Taiyuan Central Hospital from May 2021 to March 2024 were selected and randomly divided into an observation group (n=76) and a control group (n=76) using a random number table. The control group received XELOX chemotherapy, while the observation group received additional HIPEC. The general surgical conditions, recovery condions, efficacy, tumor markers [vascular endothelial growth factor (VEGF), matrix metalloproteinase-9 (MMP9), carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199)], immune function ($CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$), HMGB1, RAGE, adverse reactions, and recurrence/metastasis

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during follow-up were compared between the two groups. **Results** There were no significant differences in incision length, operation time, intraoperative blood loss, or postoperative exhaust time between the two groups (P>0.05). The total effective rate in the observation group was higher than that in the control group (88.16% *vs* 75.00%, P<0.05). After 1 and 3 cycles of chemotherapy, serum levels of CEA, VEGF, MMP9, and CA199 in the observation group were lower than those in the control group (P<0.02). After 1 and 3 cycles of chemotherapy, $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ levels in the observation group were higher than those in the control group, while $CD8^+$ levels were lower (P<0.02). Serum HMGB1 and RAGE levels in the observation group were lower than those in the control group after 1 and 3 cycles of chemotherapy (P<0.02). There was no significant difference in adverse reactions between the two groups (P>0.05). After 6 months of follow-up, the disease-free survival rate in the observation group was higher than that in the control group (93.42% *vs* 82.89%, χ^2=4.033, P<0.05). **Conclusion** HIPEC after laparoscopic surgery for colorectal cancer demonstrates good efficacy, improves immune function, and may be associated with the HMGB1/RAGE axis, without significantly increasing adverse reactions, indicating a certain level of safety.

Keywords: Colorectal cancer; Hyperthermic intraperitoneal chemotherapy; Laparoscopic surgery; High mobility group box 1; Receptor for advanced glycation end products; Safety

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结直肠癌是常见的消化道系统恶性肿瘤，其起病隐匿，多数患者确诊时已处于进展期阶段，单纯手术难以根治；腹腔镜手术是结直肠癌治疗常用术式，手术安全性较高，但术后仍存在复发、转移风险，因此术后辅助化疗尤为重要[1-2]。XELOX方案是结直肠癌常用化疗方案，通过化疗药物灭杀癌细胞，有利于抑制癌细胞增殖[3]。XELOX全身静脉化疗时，药物浓度不足以完全杀灭腹腔内癌细胞，加大药物剂量虽可一定程度提高化疗效果，但毒副作用也随之增大[4]。近年来腹腔热灌注化疗（hyperthermic intraperitoneal chemotherapy，HIPEC）逐渐应用于结直肠癌术后的辅助治疗，将化疗药物注入腹腔，可在局部维持较长时间的药物高浓度状态，直接消除脱落癌细胞或微小转移灶[5-6]。现阶段，炎症在机体细胞癌变过程中的重要作用已得到公认，但炎症通路如何发挥致癌作用尚无明确结论。高迁移率族蛋白1（high mobility group box 1，HMGB1）是一种晚期炎症因子，广泛存在于真核细胞核内，可调节基因转录，释放到胞外可介导炎症反应[7]。晚期糖基化终产物受体（receptor for advanced glycation end products，RAGE）是一种单次跨膜蛋白，属多配体的跨膜信号转导受体，当HMGB1与受体RAGE结合后，可活化下游炎症信号通路[8-9]。若能阐明HMGB1/RAGE轴在结直肠癌中的作用机制，有望为临床靶向治疗提供新思路。故本研究尝试探讨HIPEC联合腹腔镜手术调控HMGB1/RAGE轴在结直肠癌治疗中的效果及安全性。现报道如下。

1 资料与方法

1.1 一般资料 本研究前瞻性选取2021年5月至2024年3月太原市中心医院收治的152例接受腹腔镜手术治疗的结直肠癌患者，按照随机数字表法分为观察和对照组，各76例。征得医院伦理委员会批准（伦理批号：20200119）批准、患者和家属签字同意。纳入标准：符合《中国结直肠癌诊疗规范（2020年版）》诊断标准[10]；经病理检查确诊；接受腹腔镜手术治疗；术前检查无远处转移；Karnofsky评分≥70分；TNM分期Ⅲ期或腹膜癌指数（PCI）评分＜17分的Ⅳ期结直肠癌：符合腹腔镜手术、HIPEC指征；无放化疗治疗史；无HIPEC、全身静脉化疗禁忌证。排除标准：存在腹腔感染；预计生存时间＜6个月；既往腹部复杂手术史；存在明显肝、心、肾功能异常；存在肠梗阻或肠穿孔需急诊手术；合并其他恶性肿瘤；妊娠期、哺乳期女性；精神异常，无法正常沟通。

对照组男46例，女30例，年龄45～64（53.82±4.39）岁，身体质量指数（BMI）23～26（23.61±0.92）kg/m^2；结肠癌47例，直肠癌29例；肿瘤直径2.5～4.5（3.74±0.28）cm；病理类型为腺癌43例，未分化癌19例，黏液癌14例；TNM分期：Ⅲ期49例，Ⅳa期27例；PCI评分11～16（13.86±0.72）分；美国麻醉医师协会（ASA）分级Ⅰ级35例，Ⅱ级32例，Ⅲ级9例。

观察组男43例，女33例，年龄43～66（54.47±5.23）岁，BMI 21～27（23.83±1.05）kg/m^2；结肠癌42例，直肠癌34例；肿瘤直径3～5（3.80±0.31）cm；病理类型为腺癌41例，未分化癌17例，黏液癌18例；TNM分期：Ⅲ期45例，Ⅳa期31例；PCI评分12～16（14.07±0.79）分；ASA分级Ⅰ级32例，Ⅱ级34例，Ⅲ级10例。两组基线资料差异无统计学意义（P＞0.05），均衡可比。

1.2　方法　两组均进行腹腔镜根治术：术前行静吸复合麻醉，取截石位，于脐下缘做1 cm切口，建立气腹，放置腹腔镜，超声刀分离腹壁，高位结扎肠系膜下动脉，清扫淋巴结。打开腹膜，切除肿瘤和累及肠段并缝合肠管断端；采用消化道吻合器进行消化道重建；确认血运良好，冲洗腹腔，视情况决定是否放置引流管，关闭腹腔，术后采用静脉自控镇痛泵。

1.2.1　对照组　对照组行腹腔镜根治术后给予XELOX方案化疗：化疗第1 d，静脉滴注奥沙利铂（哈药集团生物工程有限公司，批准文号：H20133094）100 mg/m^2，滴注3 h；化疗第1～14 d，口服卡培他滨（南京优科制药有限公司，批准文号：H20223015）850~1000 mg/m^2，2次/d；休息1周；21 d为1个周期。化疗3个周期后进行疗效评估。

1.2.2　观察组　观察组在对照组基础上给予HIPEC，于上腹腔及盆腔各留2根灌注引流管，于术后第2天使用体腔热灌注机开始HIPEC治疗，灌注液：氟尿嘧啶（辽宁新高制药有限公司，批准文号：H21024236）2 g，0.9%氯化钠注射液4 000 mL；灌注温度43 ℃，灌注速度：100～800 mL/min。留置引流管，每2天进行1次，连续治疗3次。

1.2.3　随访　治疗后以电话、门诊等方式随访6个月，统计复发、转移及无病生存等情况。

1.3　观察指标　（1）比较两组手术情况。（2）比较两组疗效。完成3个周期治疗后进行疗效判定[11]。完全缓解：病灶完全消失并维持≥4周。部分缓解：病灶体积较治疗前缩小＞30%并维持≥4周。稳定：病灶体积缩小<30%或增大<20%。进展：病灶体积增大≥20%或出现新的病灶。总有效率=（完全缓解+部分缓解）例数/总例数×100%。（3）比较两组术前，化疗1、3个周期后肿瘤标志物。采集两组静脉血5 mL，8 cm半径3 500 r/min离心12 min取血清，酶联免疫吸附法检测糖类抗原199（CA199）、癌胚抗原（CEA）、基质金属蛋白酶9（MMP9）、血管内皮生长因子（VEGF）。（4）比较两组术前，化疗1、3个周期后免疫功能。采用流式细胞仪（美国贝克曼库尔特，FC-500型）检测T淋巴细胞亚群（血清CD3$^+$、CD4$^+$、CD8$^+$、CD4$^+$/CD8$^+$）水平。（5）比较两组术前，化疗1、3个周期后HMGB1和RAGE水平。采集两组静脉血5 mL离心分离血清，采用酶联免疫吸附法检测血清HMGB1、RAGE水平。（6）比较两组毒副反应。毒副反应分级参照WHO制订的抗癌药物常见毒副反应分级标准，分为0～Ⅳ级，级别越高，毒性越大。（7）比较两组复发、转移及无病生存等情况。

1.4　统计学方法　采用SPSS 27.0软件对数据进行分析，计量资料经正态性、方差齐性检验显示均服从正态分布且方差齐，用$\bar{x}\pm s$表示，组间比较行独立样本t检验；多时间点比较采用重复测量方差分析，若时间与处理因素之间不存在交互效应，则直接采用主效应检验评价，若存在交互效应，则通过单因素重复测量方差、多变量方差分析组内效应、组间效应。采用Bonferroni方法对检验水准α=0.05进行校正后进行两两比较。计数资料以例（%）表示，比较行χ^2检验。检验水准α=0.05。

2　结　果

2.1　两组手术情况比较　两组手术时间、切口长度、术中出血量、术后排气时间比较差异无统计学意义（P＞0.05）。见表1。

2.2　两组疗效比较　观察组总有效率高于对照组，差异有统计学意义（P＜0.05）。见表2。

2.3　两组肿瘤标志物比较　两组不同时间血清CEA、VEGF、MMP9、CA199的时间效应、组间效应、交互效应有统计学意义（P＜0.05），时间效应和组间效应进行单独效应的检验。采用Bonferroni方法对检验水准α=0.05进行校正（α'=0.02），两组不同时间血清CEA、VEGF、MMP9、CA199水平比较差异有统计学意义（P＜0.02）；多变量方差分析显示，观察组化疗1个周期后、化疗3个周期后血清CEA、VEGF、MMP9、CA199水平均低于对照组（P＜0.02）。见表3。

2.4　两组免疫功能比较　两组不同时间CD3$^+$、CD4$^+$、CD8$^+$、CD4$^+$/CD8$^+$的时间效应、组间效应、交互效应有统计学意义（P＜0.05），时间效应、组间效应进行单独检验（α'=0.02），两组不同时间CD3$^+$、CD4$^+$、CD8$^+$、

表1　两组手术情况比较　（$\bar{x}\pm s$）

Tab.1　Comparison of general surgical conditions between two groups　（$\bar{x}\pm s$）

组别	例数	手术时间（min）	切口长度（cm）	术中出血量（mL）	术后排气时间（d）
观察组	76	140.10±35.38	4.62±1.13	103.24±24.87	3.10±0.91
对照组	76	137.24±36.24	4.70±1.50	106.86±25.12	3.23±1.04
t值		0.492	0.371	0.893	0.820
P值		0.623	0.711	0.373	0.413

表2　两组疗效比较　（例）

Tab.2　Comparison of efficacy between two groups　（case）

组别	例数	完全缓解	部分缓解	稳定	进展	总有效率（%）
观察组	76	24	43	9	0	88.16
对照组	76	17	40	19	0	75.00
χ^2值						4.378
P值						0.036

$CD4^+/CD8^+$比较差异有统计学意义($P<0.02$)；多变量方差分析结果显示，观察组化疗1个周期后、化疗3个周期后$CD3^+$、$CD4^+$、$CD4^+/CD8^+$水平均高于对照组，$CD8^+$水平低于对照组($P<0.02$)。见表4。

2.5 两组HMGB1和RAGE比较 两组不同时间血清HMGB1、RAGE的时间效应、组间效应、交互效应有统计学意义($P<0.05$)，时间效应、组间效应进行单独检验($\alpha'=0.02$)，两组不同时间血清HMGB1、RAGE比较差异有统计学意义($P<0.02$)；多变量方差分析结果显示，观察组化疗1个周期后、化疗3个周期后血清HMGB1、RAGE均低于对照组($P<0.02$)。见表5。

2.6 两组毒副反应比较 两组恶心呕吐、肝功能损害、白细胞减少比较差异无统计学意义($P>0.05$)。见表6。

2.7 两组复发、转移及无病生存情况比较 随访6个月，观察组复发、转移5例，无病生存71例，对照组复发、转移13例，无病生存63例，观察组无病生存率高于对照组(93.42% *vs* 82.89%，$\chi^2=4.033$，$P<0.05$)。

表3 两组肿瘤标志物比较 ($n=76$, $\bar{x}\pm s$)

Tab.3 Comparison of tumour markers between two groups ($n=76$, $\bar{x}\pm s$)

指标	组别	术前	化疗1个周期后	化疗3个周期后
CEA(pg/mL)	观察组	28.34±5.92	17.52±3.82	4.46±1.38
	对照组	28.78±5.31	20.04±3.67	5.33±1.62
	F值	$F_{组间}=11.624$, $F_{时间}=19.622$, $F_{交互}=25.495$		
	P值	$P_{组间}<0.001$, $P_{时间}<0.001$, $P_{交互}<0.001$		
VEGF(ng/L)	观察组	648.81±130.83	497.51±96.54	403.10±81.45
	对照组	660.23±142.79	542.38±112.60	449.63±85.29
	F值	$F_{组间}=19.375$, $F_{时间}=26.388$, $F_{交互}=40.152$		
	P值	$P_{组间}<0.001$, $P_{时间}<0.001$, $P_{交互}<0.001$		
MMP9(ng/L)	观察组	583.72±120.63	367.81±93.55	294.23±73.84
	对照组	566.48±134.65	414.57±100.83	341.05±83.51
	F值	$F_{组间}=15.030$, $F_{时间}=23.659$, $F_{交互}=34.572$		
	P值	$P_{组间}<0.001$, $P_{时间}<0.001$, $P_{交互}<0.001$		
CA199(pg/mL)	观察组	26.88±3.96	20.19±3.10	18.81±2.72
	对照组	26.39±4.02	23.70±3.68	21.57±3.11
	F值	$F_{组间}=14.243$, $F_{时间}=21.165$, $F_{交互}=28.694$		
	P值	$P_{组间}<0.001$, $P_{时间}<0.001$, $P_{交互}<0.001$		

表4 两组免疫功能比较 ($n=76$, $\bar{x}\pm s$)

Tab.4 Comparison of immune function between two groups ($n=76$, $\bar{x}\pm s$)

指标	组别	术前	化疗1个周期后	化疗3个周期后
$CD3^+$(%)	观察组	50.17±4.12	61.54±5.49	71.23±6.03
	对照组	48.96±5.37	56.31±5.53	65.30±5.22
	F值	$F_{组间}=12.254$, $F_{时间}=16.257$, $F_{交互}=25.830$		
	P值	$P_{组间}<0.001$, $P_{时间}<0.001$, $P_{交互}<0.001$		
$CD4_+$(%)	观察组	31.07±3.99	38.64±4.31	43.55±4.72
	对照组	32.35±4.12	35.37±4.02	37.51±3.97
	F值	$F_{组间}=11.538$, $F_{时间}=18.433$, $F_{交互}=28.017$		
	P值	$P_{组间}<0.001$, $P_{时间}<0.001$, $P_{交互}<0.001$		
$CD8^+$(%)	观察组	30.41±3.34	23.64±2.54	21.03±2.42
	对照组	30.36±3.62	26.87±2.69	24.96±2.56
	F值	$F_{组间}=14.109$, $F_{时间}=23.064$, $F_{交互}=37.455$		
	P值	$P_{组间}<0.001$, $P_{时间}<0.001$, $P_{交互}<0.001$		
$CD4^+/CD8^+$	观察组	1.02±0.31	1.63±0.50	2.07±0.62
	对照组	1.07±0.33	1.32±0.36	1.50±0.38
	F值	$F_{组间}=9.561$, $F_{时间}=14.586$, $F_{交互}=24.348$		
	P值	$P_{组间}<0.001$, $P_{时间}<0.001$, $P_{交互}<0.001$		

表5 两组HMGB1和RAGE比较 ($n=76$, $\bar{x}\pm s$)

Tab.5 Comparison of HMGB1 and RAGE between two groups ($n=76$, $\bar{x}\pm s$)

指标	组别	术前	化疗1个周期后	化疗3个周期后
HMGB1(ng/mL)	观察组	3.19±0.95	1.27±0.34	0.86±0.24
	对照组	2.96±0.83	1.54±0.54	1.29±0.37
	F值	$F_{组间}=10.823$, $F_{时间}=13.625$, $F_{交互}=21.582$		
	P值	$P_{组间}<0.001$, $P^{时间}<0.001$, $P_{交互}<0.001$		
RAGE(pg/mL)	观察组	318.52±49.33	214.28±42.05	156.30±36.59
	对照组	309.11±47.29	257.43±47.81	188.16±41.57
	F值	$F_{组间}=17.951$, $F_{时间}=22.483$, $F_{交互}=35.038$		
	P值	$P_{组间}<0.001$, $P_{时间}<0.001$, $P_{交互}<0.001$		

表6 两组毒副反应比较 ($n=76$, 例)

Tab.6 Comparison of toxic and side effects between two groups ($n=76$, case)

组别	恶心呕吐		肝功能损害		白细胞减少	
	Ⅰ~Ⅱ级	Ⅲ~Ⅳ级	Ⅰ~Ⅱ级	Ⅲ~Ⅳ级	Ⅰ~Ⅱ级	Ⅲ~Ⅳ级
观察组	19	11	11	5	14	5
对照组	16	14	10	3	9	3
χ^2值	0.617		0.621		1.992	
P值	0.734		0.733		0.369	

3 讨 论

结直肠癌发病率在我国恶性肿瘤中位居第三，且存在逐年升高态势，每年新增患者近40万例，已成为我国重要的社会健康问题之一[12-13]。

HIPEC是新型肿瘤辅助治疗方法，可将化疗药物经灌注引流管直接送入结直肠癌患者腹腔内部，具有循环灌注、精准恒温的特点[14-15]。本研究显示，化疗1、3个周期后观察组$CD3^+$、$CD4^+$、$CD4^+/CD8^+$水平均高于对照组，$CD8^+$、血清CEA、VEGF、MMP9、CA199水平均低于对照组；相较于对照组，观察组随访期间复发转移较少，无病生存比例较高。提示HIPEC联合腹腔镜手术用于结直肠癌患者中可较好地控制疾病，利于改善机体免疫功能、调节血清内肿瘤标志物。分析HIPEC对结直肠癌的作用主要在于：能有

效提高局部药物浓度，延长肿瘤组织与高浓度药物的接触时间，准确高效地清除腹腔内残留肿瘤细胞，且避免血液循环内药物蓄积[16-17]。同时，HIPEC的热效应也能直接作用肿瘤细胞染色体，促进溶菌酶释放，增加对肿瘤细胞的溶解作用，减少血清内肿瘤标志物含量，提高疾病控制效果[18]。此外，HIPEC治疗中化疗药物还可经腹膜到达肝门静脉，一定程度提高肝内药物浓度，对结直肠癌肝转移起到控制作用[19]。结直肠癌患者受肿瘤、手术等影响，术后机体免疫功能较低，HIPEC通过热作用加快血流速度、血管扩张，有利于诱导机体抗肿瘤细胞免疫应答，改善免疫系统、增强免疫功能，进而促进肿瘤细胞凋亡，改善结直肠癌治疗预后。本研究结果显示，两组毒副反应比较差异无统计学意义。可能由于HIPEC是一种局部治疗措施，腹膜屏障功能可减慢HIPEC局部治疗过程中大分子药物的扩散吸收，以维持腹腔中的较高药物浓度，有效杀灭癌细胞；且化疗药物经肝脏代谢后再进入外周循环，有利于降低化疗药物的毒副作用[20]。

慢性炎症是肿瘤的关键特征，可促进肿瘤微环境的免疫抑制，为肿瘤发生、发展提供促瘤微环境，结直肠癌的发展与其炎症微环境联系密切。相关研究表明，HMGB1、RAGE结合后可参与多种肿瘤细胞的增殖、侵袭[21]。杨红玉等[22]研究显示，早期宫颈癌患者血清HMGB-1、RAGE与肿瘤恶性生物学行为相关因子Caspase-3、Bcl-2、MMP1水平呈正相关关系。易正洪等[23]报道显示，HMGB1过表达可一定程度逆转绞股蓝皂苷对骨肉瘤细胞恶性生物学行为的抑制作用。本研究结果显示，观察组总有效率较对照组更高，观察组化疗1个周期后、化疗3个周期后血清HMGB1、RAGE均低于对照组。可见结直肠癌细胞中存在HMGB1、RAGE蛋白的高表达，下调HMGB1、RAGE表达可能有利于提高结直肠癌治疗效果。经分析，HMGB1/RAGE轴的作用机制可能涉及炎症、免疫调节和化疗敏感性调控，结直肠癌患者机体慢性炎症可上调HMGB1、RAGE蛋白表达，HMGB1、RAGE大量释放又可增强局部炎症反应，激活RAS信号途径下游的转录共激活因子，HMGB1/RAGE轴在结直肠癌中通过炎症信号刺激肿瘤细胞增殖[24-25]。HIPEC联合腹腔镜手术可能通过HMGB1/RAGE轴调节肿瘤微环境，激活免疫系统，拮抗细胞增殖，诱导肿瘤细胞凋亡。HIPEC应用于结直肠癌腹腔镜术后，一方面，HIPEC腹腔内给药使高浓度化疗药物直接作用于残留肿瘤组织，其高浓度药效的肿瘤消杀作用较循环途径给药明显增强[26-27]。另外，HIPEC的高温作用可提升癌细胞内溶酶体活性，破坏癌细胞的稳定性，减少残余肿瘤负荷，HIPEC联合腹腔镜手术可协同增强抗肿瘤免疫，可能通过下调HMGB1、RAGE表达抑制肿瘤相关的炎症反应，进而提高治疗效果[28]。

综上所述，HIPEC联合腹腔镜手术可有效改善结直肠癌患者免疫功能，有利于调节肿瘤标志物水平，可能通过HMGB1/RAGE轴发挥作用，提高治疗效果，且具有一定安全性。

利益冲突　无

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(上接第1019页)

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