MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2016; 22: 4205-4209
DOI: 10.12659/MSM.897842

Received: 2016.01.30
Accepted: 2016.03.16
Published: 2016.11.06

Effect of Splenectomy Combined with Resection for Gastric Carcinoma on Patient Prognosis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Source of support: Departmental sources

Background: For patients with stage IV gastric cancer, it is unclear whether splenectomy combined with palliative surgery is needed to reduce tumor load and relieve symptoms. The objective of the present study was to investigate the effect of splenectomy combined with palliative resection for stage IV gastric carcinoma on immunological dysfunction and patient prognosis.

Material/Methods: We retrospectively analyzed medical records of 106 stage IV gastric cancer patients who underwent palliative surgery; of these, 49 patients were treated with palliative resection for gastric carcinoma combined with splenectomy, while the other 57 patients retained their spleens. The immunologic function and prognosis in these 2 groups were examined and compared.

Results: The immune function of patients in the group that retained their spleens was better later in the postoperative course than in the resection group. The groups did not show statistically significant differences in postoperative infectious complications, median survival time, and survival rate; however, the average postoperative hospitalization time of patients in the retained group was significantly shorter.

Conclusions: Splenectomy combined with gastric cancer resection did not improve the prognosis of the patients; patients who retained their spleens had faster recovery and improved immune function. However, whether retaining the spleen is an independent factor improving the prognosis needs further investigation.

MeSH Keywords: Prognosis • Splenectomy • Stomach Neoplasms

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/897842

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Background

Gastric cancer is one of the most common gastrointestinal malignancies; the World Health Organization ranks it fourth worldwide and third in China as a cause of cancer-related morbidity and mortality [1]. D2 radical gastrectomy is the best therapeutic option for patients with stage II and III gastric cancer [2,3], and splenectomy combined with gastrectomy does not meaningfully improve patient prognosis [4]. However, for patients with stage IV gastric cancer, it is still unclear whether splenectomy combined with palliative surgery is needed to reduce tumor load and relieve symptoms such as obstruction and bleeding [5–7]. As the most important peripheral immune organ, the spleen plays a negative immunologic role in advanced-stage cancer [8]. However, its anti-tumor function is incomplete and bidirectional; the spleen has a positive anti-tumor role in the early stage of tumor formation, but this effect diminishes over time, even has a negative immunological influence with tumor progression [9–11]. The present study investigated the effect of splenectomy combined with palliative resection for gastric carcinoma on the immunological dysfunction and prognosis of stage IV gastric cancer patients. We retrospectively analyzed 106 stage IV gastric cancer patients who underwent palliative surgery, and explored the influence splenectomy combined with palliative resection for gastric carcinoma on immune function and patient prognosis.

Material and methods

Our study enrolled 106 patients with gastric cancer. Age at presentation ranged from 29 to 79 years (mean age 58.6 years). Sixty-seven of the patients were males and 39 were females. According to the Gastric Cancer Guidelines Diagnostic Criteria of the National Comprehensive Cancer Network (NCCN) in 2014, these patients were diagnosed with stage IV gastric cancer. Preoperative and intraoperative examinations found that their liver, lungs, enterocoele, or pelvic cavity were involved. Adenocarcinoma (71 patients) and signet-ring cell carcinoma (35 patients) were diagnosed in the postoperative pathologic examination. Out of the total of 106 patients, 49 underwent splenectomy (SE group); among these 49 patients, 31 were males and 18 were females, mean age was 58.1±11.0 years, and mean body weight was 62.3±10.8 Kg. Spleen removal in 33 patients was due to invasion by tumor cells, and palliative resection of the stomach combined with splenectomy was performed in 16 patients due to spleen lesions. The other 57 patients retained their spleens (RS group); 38 were males and 21 were females, mean age was 59.3±11.2 years, and mean body weight was 60.8±9.1 Kg. All of these 38 patients underwent palliative total gastrectomy. The SE and RS groups were similar in sex, age, and body weight. Six or more courses of chemotherapy using mDCF (modified docetaxel, cisplatin, and fluorouracil) or FOLFOX4 (fluorouracil, leucovorin, and oxaliplatin) were implemented after surgery. The healthy control group contained 20 normal and healthy examinees (12 males and 8 females, mean age 57.7±13.1 years, and mean body weight 65.7±8.1 Kg).

Inclusion criteria were: (1) stage IV gastric cancer, (2) normal hepatic and renal function before surgery, and (3) no immunopotentiator or immunosuppressor administered within half a year before surgery. Exclusion criteria were: (1) underwent 2-stage radical therapy using excision or radiofrequency ablation (PRFA) postoperatively for metastatic lesions of the liver or lung; (2) severe complications such as hemorrhage or anastomotic leakage and underwent a 2-stage operation after the first surgery; (3) chemotherapy was not implemented postoperatively; (4) survival time less than 6 months postoperatively; (5) liver cirrhosis or portal hypertension hypersplenism; (6) cardiovascular disease such as cardiac insufficiency or level-3 hypertension; (7) severe diabetes; and (8) hematopoietic system with chronic disease, including moderate or severe anemia, lymphoma, or HIV-infected patients.

Monitoring index

Peripheral blood immunoglobulin (IgA, IgG, and IgM) and T-lymphocyte subsets (CD4, CD8, and CD3) in the 2 surgical group and the healthy control group were tested before the operation and at 10 days, 6 months, and 12 months postoperatively. Blood immunoglobulin was detected using an Array360 device, and T lymphocyte subsets were tested using a Beckman-Coulter Epics XL flow cytometer. The biochemical index was determined. We recorded data on duration of surgery, intraoperative hemorrhaging, incidence of postoperative infectious complications (abdominal infection, incisional wound infection, and pulmonary infection), hospitalization duration postoperatively (HDP), median survival time, and survival rate.

Statistical method

Statistical analysis of all data was performed using SPSS (Statistical Product and Service Solutions) Version 18.0 software. Measurement data are shown as $\bar{\chi}$±S. We used the independent-samples *t* test and the χ^2 test for enumeration data. P<0.05 represented a significant difference.

Results

Immunologic function of patients in SE and RS groups

We found no significant difference between the SE group and RS group in cellular immunologic function (CD3, CD4, CD8, and CD4/CD8) or humoral immune function (t = 0.221, 1.011,

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Table 1. Immune function of patients in SE and RS groups.

Index	Health control	SE group				RS group			
		Pre	10 d	6 m	12 m	Pre	10 d	6 m	12 m
CD3	68.24±5.24	54.91±11. 2	57.76±7.41	53.01±11.29	45.66±11.95	54.46±9.82	59.95±7.57	60.39±9.17	52.01±7.32
CD4	38.42±3.96	33.79±8.41	37.08±7.77	33.81±6.49	29.29±6.0	32.36±6.17	38.09±6.28	38.66±5.88	34.88±5.78
CD8	21.22±2.09	23.64±5.44	24.21±6.85	26.11±5.14	29.86±5.29	24.91±5.36	23.61±5.37	23.53±3.99	25.36±5.49
CD4/CD8	1.76±0.13	1.43±0.25	1.54±0.26	1.30±0.26	1.06±0.21	1.31±0.30	1.58±0.26	1.59±0.25	1.38±0.28
IgG	11.34±2.30	7.61±2.17	9.94±1.60	7.08±2.21	6.10±1.94	7.10±2.17	10.1±2.19	9.45±2.15	7.16±1.81
IgA	2.13±0.60	1.11±0.42	1.64±0.43	1.27±0.46	1.02±0.32	1.06±0.53	1.76±0.57	1.65±0.64	1.26±0.50
IgM	1.84±0.47	0.92±0.37	1.24±0.37	0.84±0.36	0.66±0.28	0.87±0.43	1.25±0.58	1.24±0.55	0.88±0.34

Table 2. Postoperative complications and prognosis.

Groups	Complications (cases, %)	Average HDP (day)	Median survival duration (month)	Survival rate at 1 year postoperation (%)
SE	12 (22.4)	15.96±5.43	12.90±4.15	61.22
RS	11 (21.1)	13.77±3.56	14.47±4.31	73.68
Statistic	χ^2=0.03	t=2.48	t=1.91	χ^2=1.88
P value	>0.05	<0.05	>0.05	>0.05

1.213, 2.248, 1.207, 0.520, 0.601; P>0.05). We found a significant difference between the surgical groups and health control group in the immunologic index (t_{SE}=6.112, 2.822, 2.327, 6.557, 7.242, 8.954, 9.676, and P<0.05; t_{RS}=7.159, 4.871, 3.626, 7.891, 8.487, 8.622, 9.644, and P<0.05).

At 10 days postoperatively, the immunologic index still did not show a difference between the SE and RS groups (t=1.497, 0.737, 0.506, 0.654, 0.438, 1.182, 0.058; and P>0.05). When compared with the index preoperatively, nearly all immune indexes in the SE group were restored and showed a statistically significant difference, except for CD3 and CD8 (t_{SE}=2.011, 2.221, 6.044, 6.245, 4.317; and P<0.05). The immune indexes in the RS group also increased and were significantly different than before the operation, except for CD8 (t_{RS}=3.344, 4.913, 5.182, 7.35, 6.822; and P<0.05).

At 6 months after the operation, we found that all of the immune indexes of the SE group were significantly lower than in the RS group (t=3.711, 4.041, 2.899, 5.863, 5.586, 3.457, 4.562; and P<0.05). When compared with 10 days after the operation, there was a significant difference in all immune functions in the SE group at 6 months (except for CD8) (t=2.461, 2.267, 4.589, 7.319, 4.097, 5.803; P<0.05). In contrast, the immune function of the RS group did not show any significant change during this period (t=0.283, 0.502, 0.080, 0.294, 1.604, 0.960, 0.020; P>0.05).

At 12 months after the operation, the immune index of the SE group was significantly lower than in the RS group (t=2.583, 3.515, 4.609, 2.104, 2.006, 2.596; P<0.05), except for CD8, which was similar. When we again compared the same index at 6 months and 12 months, the immune function of patients in the SE group further decreased (t=2.414, 2.677, 3.797, 2.247, 2.178; P<0.05), while the SR group had slightly decreased immune function (t=4.887, 3.186, 1.919, 3.955, 5.616, 3.286, 3.736; P<0.05) (Table 1).

Postoperative complications and prognosis

There were no significant differences in infectious complications (abdominal infection, incisional wound infection, and pulmonary infection) between groups; the median survival time and survival rate at 1 year after the operation in the SE group were obviously better than in the RS group, but the difference was not statistically significant (P>0.05). Average length of stay (LOS) in the SE group was significantly shorter than in the RS group (P<0.05) (Table 2).

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Discussion

Immune function of patients with stage IV gastric cancer was reduced, as shown by evidence that the immune indexes of the surgical groups were lower than in the healthy control group. However, mid-term and long-term follow-up results fail to clearly show whether immunologic function can be restored after the primary lesion is palliatively removed. As the most important peripheral immune organ, the spleen plays a negative immunologic role in advanced-stage cancer. Thus, it is unclear if gastrectomy combined with resection of the spleen is effective, especially when the primary tumors were palliatively resected.

A report by Chu et al. reported a negative immunologic effect on advanced tumors, suggesting that superoxide anion, which is produced by macrophages to kill tumor cells, is not be stimulated by tuftsin secreted by the spleen within the course of tumor progression [12]. Zhang et al. observed changes in splenic macrophages in a model of pulmonary metastasis of liver cancer by applying diethylnitrosamine, and also found that phagocytosis, metabolism, secretion, and antigen presentation function of splenic macrophages were generally reduced [13]. In research on small cell lung cancer, Levy et al. reported that the proliferation and metastasis of advanced tumors are suppressed after splenectomy [14]. Isik et al. demonstrated that because the metastatic lymph node ratio is decreased by resecting the perisplenic lymph nodes, survival may be increased by splenectomy [15,16]. A similar phenomenon was also reported in a study of diffuse large B cell lymphoma [17]. Wang et al. suggested that the low level of IgE and IgM caused by polycyclic aromatic hydrocarbons induced cancer and precancerous lesions in the stomach [18]. Nevertheless, our results in the present study suggest that the immune function of patients in the SE group was reduced at 6 months after the operation compared with 10 days after the operation, and there were no significant differences between these 2 time points in the RS group. The immunologic index of both groups were reduced at 12 months after the operation, but the immune functions of the RS group still preceded the SE group, which may be attributable to the anti-tumor effect of the spleen. Additionally, the median survival time of RS group patients was longer, and survival rate at 1 year was also higher than in SE group patients, but the difference was not statistically significant.

We speculate that the negative immunological role of the spleen in advanced-stage cancer could be due to the emergence of an immune suppressor secreted from tumor cells, such as vascular endothelial growth factor (VEGF) or prostaglandin E2 (PGE2) [19]; the tumor itself is the primary cause of immune suppression, and the spleen passively participates in the formation of the suppression. The immune functions of patients in the 2 surgical groups in the present study were increased after the tumors were resected palliatively, suggesting that the anti-tumor effect of immunologic function of the spleen was restored when the negative factor resulting in immune suppression produced by tumor cells was eliminated and the suppression was released. Flak et al. studied the immunohistochemistry of spleen specimens obtained from stomach cancer surgery, and found that the structure did not change in the immunogenic region of the spleen, but there was a quantitative change and dysfunction of immunocytes [20]. Moreover, Yao et al. determined the essential role of loss of activity of killer cells and quantity of CD25 cells in tumor progression by using a liver cancer and spleen resection mouse model in the study of the host anti-tumor immunologic function [21], which supports our hypothesis.

Conclusions

For patients with uncurable stage IV gastric cancer, palliative resection of primary tumors can promote quality of life, provide short-term improvement of immune function, and prolong survival time. Splenectomy combined with gastrectomy does not improve the prognosis, and patients who retain their spleens have faster recovery and improved immune function. However, whether retaining the spleen is an independent factor in improving prognosis needs further investigation with more cases and longer follow-up time.

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