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Evaluation of Postoperative Outcomes of Endoscopic Submucosal Dissection in Primary Gastric Cancer

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Abstract

Background: Few studies have investigated the changes in postoperative quality of life; serum Livin, epidermal growth factor (EGF), and interleukin (IL)-8 levels; and traumatic stress in patients with early gastric carcinoma after endoscopic submucosal dissection.
Objectives: We aimed to determine the effect of endoscopic submucosal dissection on postoperative life satisfaction and serum Livin, EGF, and IL-8 levels in early gastric carcinoma patients.
Methods: Seventy-three early gastric carcinoma patients were divided into the control (n = 35, traditional radical surgery) and case (n = 38, endoscopic submucosal dissection) groups based on surgical approaches.
Results: The operative time, gastrointestinal recovery time, length of hospital stay, perioperative bleeding, EuroQol visual analog scale scores, gastrin, and motilin levels were significantly superior to those in the control group, whereas serum Livin, EGF, IL-8, and C-reactive protein levels, as well as the total incidence of postoperative complications, were significantly lower in the case group than in the control group (all $P < 0.05$).
Conclusion: Endoscopic submucosal dissection in early gastric carcinoma patients provides the advantages of a short operative time, less perioperative bleeding, rapid postoperative recovery, and less traumatic stress and postoperative complications, as well as reduced serum Livin, EGF, IL-8, and tumor marker levels.

Keywords: Early gastric carcinoma, EGF, Endoscopic submucosal dissection, IL-8, Livin1

1. Background

In early gastric carcinoma, the tumor lesions have infiltrated only the inner mucosa or submucosa. The advancements in medical technology have made it easier to detect early gastric carcinoma. Therefore, surgery is often the first treatment of choice. Clinical studies have shown that patients with early gastric carcinoma exhibit a 5-year survival rate of up to 90% and a better prognosis after radical surgery (1, 2). However, traditional laparotomy causes severe trauma, negatively impacts gastrointestinal function, and is associated with numerous postoperative complications (3). Endoscopic submucosal dissection, an emerging minimally invasive procedure, helps avoid severe trauma and ensures minimally invasive treatment. Many studies have suggested that endoscopic submucosal dissection is an effective treatment for early gastric carcinoma resulting in a better long-term prognosis (4-6). However, a study has reported that endoscopic submucosal dissection in 1159 patients with early gastric carcinoma was significantly associated with regional metastasis, invasion, and differentiation of early gastric carcinoma. Therefore, it is necessary to master the indications for endoscopic submucosal dissection to ensure a safe procedure.

Livin, a type of anti-apoptotic factor, is specifically highly expressed in early gastric carcinoma and may be essential in promoting the occurrence, invasion, differentiation, and metastasis of gastric carcinoma. Epidermal growth factor (EGF) is a member of the growth factor family. When gastric carcinoma occurs, serum EGF is overexpressed, which may be an essential indicator for the progression and prognosis of gastric carcinoma. Interleukin (IL)-8 is a member of the chemokine family and is highly expressed in gastric carcinoma tissues and serum of gastric carcinoma patients, which may be an essential indicator for assessing the occurrence, depth of infiltration and differentiation of gastric carcinoma. Nevertheless, few studies have investigated the changes in postoperative quality of life, serum Livin, EGF, and IL-8 levels, and traumatic stress in patients with early gastric carcinoma after endoscopic submucosal dissection.

2. Objectives

In this study, the therapeutic effects of endoscopic submucosal dissection for the treatment of early gastric carcinoma were investigated in terms of curative effects, serum cytokine levels,

traumatic stress levels, postoperative quality of life, and other aspects.

3. Methods

3.1. General information

Seventy-three patients with early gastric carcinoma admitted to our hospital from January 2016 to December 2016 were enrolled in the study. The inclusion criteria included patients who (1) were pathologically classified with moderately or highly differentiated adenocarcinoma with a maximum tumor diameter ≤ 2 cm, (2)were newly diagnosed, (3) did not have a history of other cancers, (4) did not have any surgical contraindications, and (5) signed the informed consent. In addition, patients who (1) had a history of gastrointestinal surgery; (2) had peripheral organ infiltration, and lymphatic metastases; (3) had hepatic, pulmonary, or renal dysfunction; (4) had experienced acute attacks of cardiovascular and cerebrovascular diseases over the past three months; or (5) were pregnant were excluded from the study. According to different surgical methods, 35 patients undergoing traditional radical surgery were assigned to the control group, and 38 patients undergoing endoscopic submucosal dissection were assigned to the case group. The Beijing First Hospital approved this Integrated Traditional Chinese and Western Medicine study. All patients provided written informed consent.

3.2. Methods

Patients in the control group underwent traditional radical surgery. After eight hours of fasting for solids and liquids, general anesthesia was administered, followed by a conventional incision at the upper abdomen to perform proximal and distal gastrectomies according to the tumor's location; then, intra-abdominal anastomosis was performed layer-by-layer. Postoperatively, the patients were given antibiotics and fasted for > 24 h. A liquid diet was allowed only after abdominal ventilation.

Patients in the case group underwent endoscopic submucosal dissection. They fasted for solids and liquids before surgery. The tumor location was confirmed using computed tomography (CT) just before surgery. Then 10 – 15 min before surgery, the patient was injected with 0.5 mg atropine intramuscularly and given 2 % lidocaine mucilage orally. After intravenous anesthesia with 1.2 mg/kg propofol, the patient was placed in the left lateral position. An ED3440T dual-channel endoscopic instrument was inserted orally into the stomach to determine the position and size of the tumor. The incisal margin was marked with an argon nozzle. Around the incisal margin, methylene blue + glycerol fructose was injected at a margin of 1 cm from the lesion; it raised the lesion, following which the mucosa was separated from the muscular layer. The lesions were cut using a HOOK knife and separated using an IT knife into the snare. The completely excised lesion was then removed. Electric coagulation hemostasis was used at the wound surface. Postoperatively, the patient was asked to fast for > 24 h until abdominal ventilation, following which a liquid diet was allowed. Routine antibiotic treatment was prescribed postoperatively.

3.3. Observed indicators

Intraoperative and postoperative conditions: operative time, perioperative bleeding, gastrointestinal recovery time, length of hospital stay, and proximal tumor margin were assessed and compared between the two groups (1). Venous blood (5 ml) collected three days before and after surgery. The separated serum was then used to determine Livin, EGF, and IL-8 levels using enzyme-linked immunosorbent assay (ELISA) kits from R&D Systems (Minneapolis, MN, USA) (2). The separated serum was also used to determine C-reactive protein (CRP), gastrin (GAS), and motilin (MTL) levels using ELISA (R&D Systems, Minneapolis, MN, USA) (3). Additionally, the separated serum was used to determine CA199 and CA724 levels using the 2010 Electrochemical Luminescence instrument and corollary reagents (4). MG7-Ag levels were measured using ELISA with a kit from R&D Systems (Minneapolis, MN, USA) (5). Quality of life and health status: before surgery and one week and three months after surgery, the patients' overall quality of life was assessed using EORTC QLQ-C30 with four dimensions, including physical functioning (12 items), psycho-spiritual (8 items), social relationship (4 items) and treatment (3 items), with a total of 27 items, and each assigned a score of 1-5. Reliability test Cronbach's α=0.79. The overall quality of life was evaluated on a scale of 100, with a higher score indicating a better quality of life. The patients' health status was evaluated using the EuroQol visual analog scale (EQ-VAS) subscale of the European Five-Dimensional Health Scale, consisting of the EQ-5D health description system and the EQ-VAS, with five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with three levels (no problems, some problems, and extreme problems. A higher score (100 points in total) indicates a better state of health (6). Safety: postoperative complications were observed in both groups. Survival and recurrence rates: postoperative health records were established for all patients, and continuous follow-up was conducted during the regular review. The 3- and 5-year survival rates and the 5-year recurrence rates were compared between the two groups; Recurrence was confirmed when the findings of endoscopy, magnetic resonance imaging, CT, etc. showed the existence of new lesions or lesions *in situ* (7).

3.4. Statistical analysis

Statistical Package for Social Sciences (SPSS) 25.0 statistical software (IBM, Armonk, NY, USA) was used for statistical analysis. Measurement data were analyzed using a t-test and are expressed as $\bar{x} \pm$ standard deviation (SD), whereas enumeration data were analyzed using the $\chi 2$ test and are expressed as percentages. $P < 0.05$ indicates statistical significance.

4. Results

4.1. Demographic and Clinical data

Comparison of gender, age, location and diameter of the tumors, and pathological types between the two groups did not show any significant differences ($P > 0.05$), as Table 1 shows.

4.2. Intraoperative and postoperative conditions

Operative time, gastrointestinal recovery time, length of hospital stay, and perioperative bleeding in the case group were superior to those in the control group ($P < 0.05$). There was no significant difference between the groups in proximal tumor margin ($P > 0.05$). Endoscopic submucosal dissection significantly shortened the operative time, promoted the recovery of gastrointestinal function, and reduced perioperative bleeding and length of hospital stay (Figure 1, Table 2).

4.3. Serum Livin, EGF, and IL-8 levels

Postoperatively, these levels decreased in both the groups, with the levels being significantly lower in the case group than in the control group ($P < 0.05$). These results suggest that endoscopic submucosal

Table 1. General information of the two groups ($\bar{x} \pm$ s, n)

Group	*n*	Gender		Average age (years)	Tumor location			Diameter of the tumor (mm)	Pathological type	
		Male	Female		Upper stomach	Central stomach	Lower stomach		Inner mucosa	Submucosa
Case	38	26	12	46.89 ± 5.45	5	13	20	15.03 ± 4.57	28	10
Control	35	25	10	47.20 ± 5.33	7	11	17	15.46 ± 4.32	26	9
P		0.780		0.807		0.733		0.681	0.953	

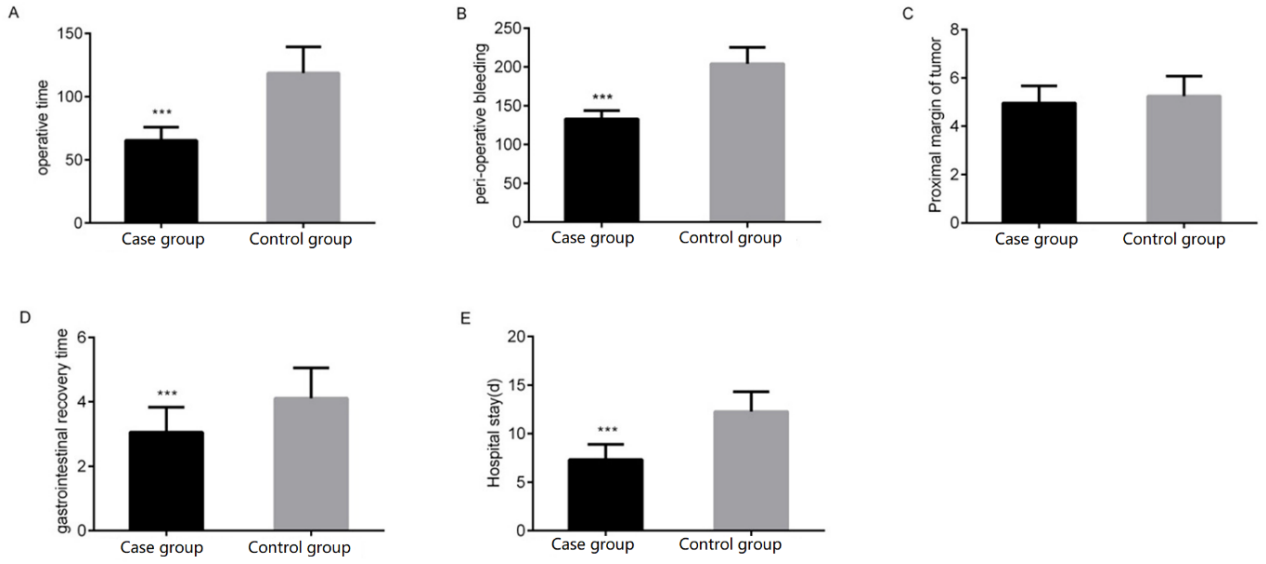

Figure 1. Comparison of intra- and postoperative conditions in both groups ($\bar{x} \pm$ s). Note: $^{***}P < 0.001$, compared with the control group

Table 2. Comparison of intra- and postoperative conditions in both groups ($\bar{x} \pm$ s).

Group	*n*	Operative time (min)	Perioperative bleeding (ml)	Proximal tumor margin (cm)	Gastrointestinal recovery time (d)	Length of hospital stay, (d)
Case	38	65.34±10.49	132.88±10.75	4.96±0.71	3.06±0.78	7.32±1.57
Control	35	118.68±20.62	203.96±21.23	5.25±0.83	4.11±0.95	12.28±2.04
P		<0.001	<0.001	0.112	<0.001	<0.001

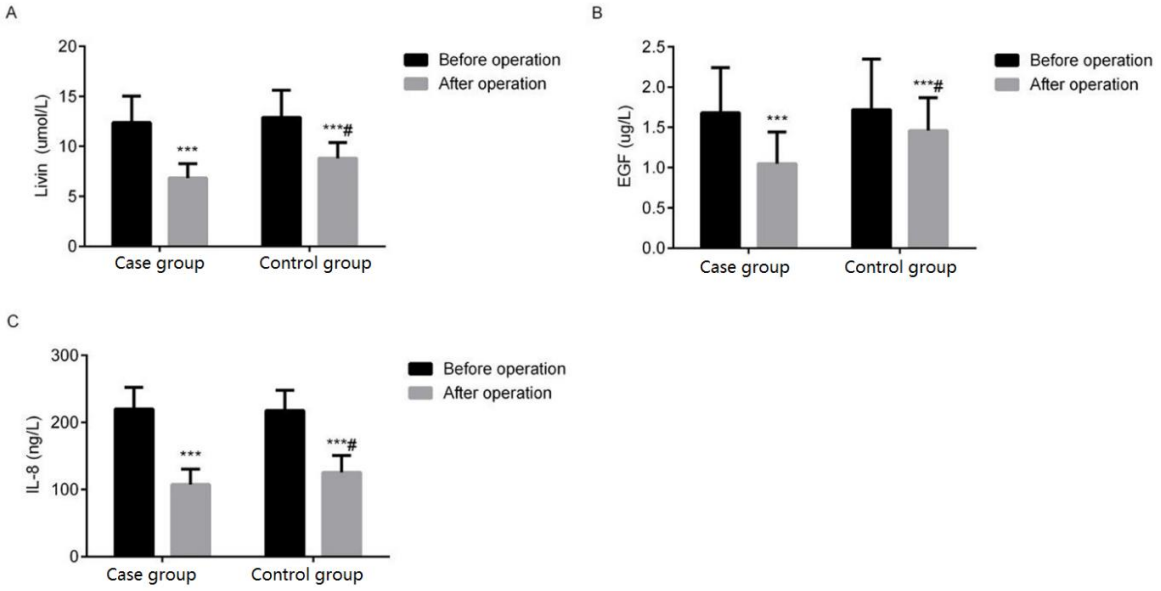

Figure 2. Comparison of serum Livin, EGF, and IL-8 levels after the operation in both groups ($\bar{x}\pm s$). Note: ***P < 0.001, compared with those before the operation; #P < 0.05, compared with the control group

dissection provides better outcomes regarding decreased serum Livin, EGF, and IL-8 levels (Figure 2, Table 3).

4.4. Traumatic stress indicator levels

Postoperatively, serum CRP levels increased and serum GAS and MTL levels decreased in the two groups, although CRP levels were lower and GAS and MTL levels were higher in the case group than in the control group ($P < 0.05$). This suggests that traumatic stress is decreased in patients who undergo endoscopic submucosal dissection (Figure 3, Table 4).

Table 3. Comparison of serum Livin, EGF, and IL-8 levels after the operation in both groups ($\bar{x}\pm s$)

Group	*n*	Livin (μmol/L)		EGF (μg/L)		IL-8 (ng/L)	
		Before	After	Before	After	Before	After
Case	38	12.38±2.65	6.85±1.43	1.68±0.56	1.05±0.39	220.16±32.28	107.35±23.27
Control	35	12.91±2.72	8.82±1.57	1.72±0.63	1.46±0.41	217.74±30.34	125.26±25.32
P		0.402	<0.001	0.775	<0.001	0.743	<0.001

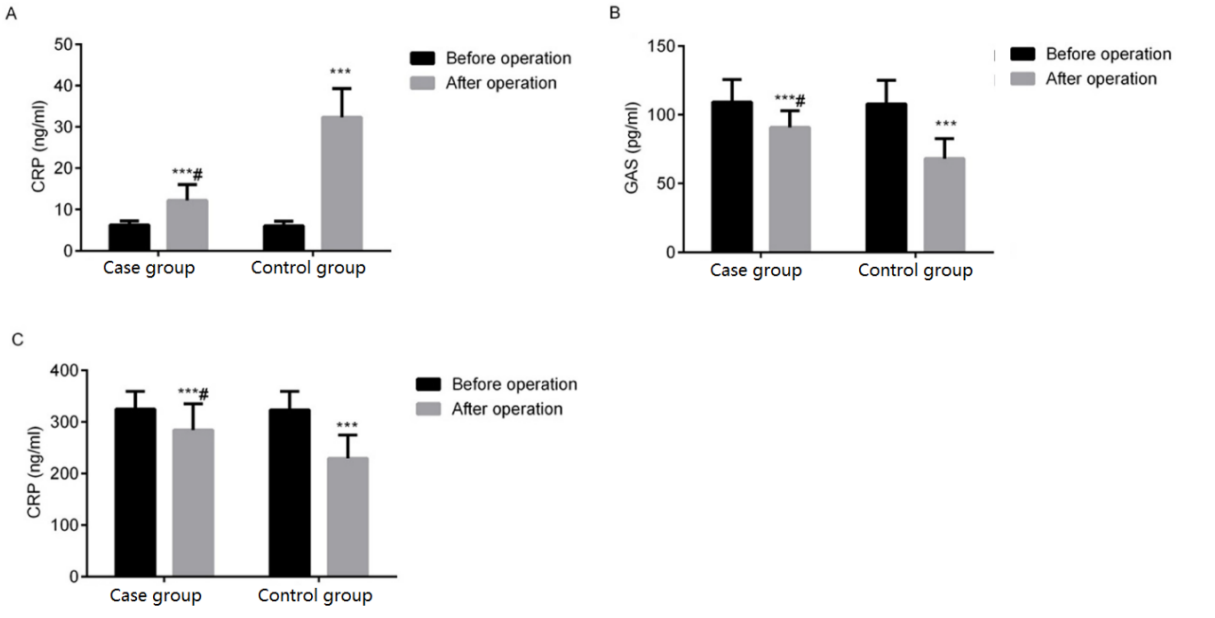

Figure 3. Comparison of traumatic stress indicators before and after the operation in both groups ($\bar{x}\pm s$). Note: ***P < 0.001, compared with those before the operation; #P < 0.05, compared with the control group

Table 4. Comparison of traumatic stress indicators before and after the operation in both groups (x̄± s).

Group	*n*	CRP (ng/ml)		GAS (pg/ml)		MTL (pg/ml)	
		Before	After	Before	After	Before	After
Case	38	6.21±1.03	12.23±3.77	109.37±16.24	90.85±12.09	325.01±34.28	284.58±50.48
Control	35	6.08±1.12	32.36±6.94	107.90±17.21	68.17±14.46	323.64±35.62	229.36±45.13
P		0.607	<0.001	0.708	<0.001	0.868	<0.001

4.5. Serum tumor marker levels

Preoperatively, CA199, CA724, and MG7-Ag levels were not significantly different between the two groups ($P > 0.05$); postoperatively, these levels were reduced in both groups. However, the CA199, CA724, and MG7-Ag levels in the case group were significantly lower than those in the control group ($P < 0.05$), indicating that endoscopic submucosal dissection significantly lowered serum tumor marker levels (Figure 4, Table 5).

4.6. Quality of life and health status

Compared with the scores before surgery, one week and three months after surgery, the EORTC QLQ-C30 and EQ-VAS scores in both groups decreased and then increased ($P < 0.05$), although the 1-week scores were higher in the case group than in the control group ($P < 0.05$). These results indicate that patients undergoing endoscopic submucosal dissection recover sooner and have a better quality of life and health (Table 6).

4.7. Postoperative complications

The total incidence of postoperative complications in the case group (7.89%) was lower than that in the control group (31.42%; $P < 0.05$), as shown in Table 7.

4.8. Postoperative survival and recurrence rates

Patients in the case group were followed up for 3.5-6 years, with a median follow-up time of 4.7

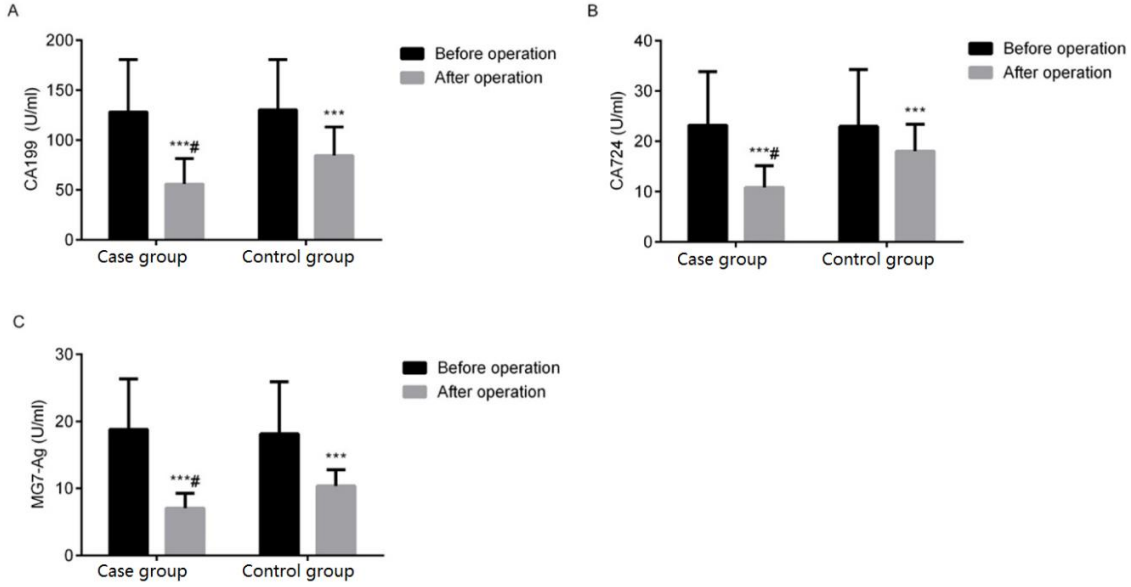

Figure 4. Comparison of serum tumor markers in both groups (x̄± s, U/ml). Note: ***P < 0.001, compared with those before operation; #P < 0.05, compared with the control group

Table 5. Comparison of serum tumor markers in both groups (x̄± s, U/ml).

Group	*n*	CA199 (U/ml)		CA724 (U/ml)		MG7-Ag (U/ml)	
		Before	After	Before	After	Before	After
Case	38	128.24±52.38	55.89±25.76	23.18±10.69	10.85±4.27	18.79±7.54	7.03±2.24
Control	35	130.17±50.59	84.62±28.49	22.96±11.34	18.06±5.35	18.13±7.78	10.36±2.39
P		0.873	<0.001	0.932	<0.001	0.714	<0.001

Table 6. Comparison of quality of life and health status before and after surgery in both groups (x̄± s, points)

Group	*n*	EORTC QLQ-C30			EQ-VAS		
		Before	1 week after	3 months after	Before	1 week after	3 months after
Case	38	67.65 ± 8.52	52.34 ± 6.90	79.27 ± 8.02	70.89 ± 8.23	63.37 ± 5.20	82.01 ± 8.45
Control	35	65.37 ± 9.21	40.75 ± 7.73	77.12 ± 9.36	71.24 ± 8.65	56.49 ± 5.31	80.89 ± 9.74
P		0.276	<0.001	0.294	0.860	<0.001	0.601

Table 7. Comparison of postoperative complications in both groups (*n* (%))

Group	*n*	Bleeding	Infection	Adhesion	Nausea/Emesis	Total incidence
Case	38	1 (2.63)	1 (2.63)	0 (0.00)	1 (2.63)	3 (7.89)
Control	35	3 (8.57)	2 (5.71)	2 (5.71)	4 (11.43)	11 (31.42)
P						0.011

Table 8. Comparison of survival and recurrence in both groups (*n* (%))

Group	*n*	3-year survival rate	5-year survival rate	Total 5-year recurrence rate
Case	38	38 (100.00)	37 (97.37)	4 (10.53)
Control	35	35 (100.00)	34 (97.14)	2 (5.71)
P		1.000	1.000	0.455

years, and those in the control group were followed up for 3.7-6.2 years, with a median follow-up time of 4.5 years. The differences in 3- (100% vs.100%) or 5-year (97.37% vs. 97.14%) survival rates and 5-year recurrence rates (10.53% vs. 5.71%) were not significantly different between the case and control groups ($P > 0.05$) as shown in Table 8.

5. Discussion

Gastric carcinoma, a common malignant tumor of the digestive system, is associated with a mortality rate of 23.2% (7). Moreover, the incidence of gastric carcinoma is increasing in China (8). Therefore, early gastric carcinoma is often treated surgically to eradicate the lesion, prolong the patient's life, and prevent recurrence (9). Applicable surgical methods include endoscopic submucosal dissection, traditional laparotomy, and endoscopic mucosal resection. Endoscopic submucosal dissection was first applied in clinical practice in 2006. Since then, it has become popular and is widely used in China. This study was conducted to observe endoscopic submucosal dissection's efficacy in treating patients with early gastric carcinoma. The results showed that the procedure had the advantages of shorter operative time, less perioperative bleeding, rapid postoperative recovery, less traumatic stress, and postoperative complications, as well as reduced serum Livin, EGF, IL-8 levels, and tumor marker levels, and the long-term postoperative prognosis of endoscopic submucosal dissection is not significantly different from that of traditional radical surgery.

Endoscopic submucosal dissection is an advanced endoscopic technique that enables curative resection of superficial lesions in the gastrointestinal tract, allowing the complete resection of lesions with negative margins while avoiding surgery and preserving organ. Compared with traditional endoscopic mucosal resection, it allows the complete resection of lesions larger than 2 cm in diameter, avoiding segmental resection and thus local recurrence. In addition, histopathological analysis of the whole lesion can be performed after its resection to determine if it is a curative resection. As shown by the results of this study, the operative time, gastrointestinal recovery time, hospital stay, and perioperative bleeding in the case group were superior to those in the control group. There was no significant difference between the groups in proximal tumor margin. In addition, the total incidence of postoperative complications in the case group was lower than that in the control group, which is consistent with previous reports (10). These results demonstrate that endoscopic submucosal dissection not only covers the same excision extension as the traditional radical resection but also shortens the operative time, reduces perioperative bleeding and postoperative complications and the length of hospital stay, and is a safe and advantageous procedure.

Livin is highly expressed in some solid tumors; it inhibits apoptosis by inhibiting the release of apoptotic factors (11). Studies have found that Livin is specifically highly expressed in early gastric carcinoma and is involved in its occurrence and progression in tumor invasion, differentiation, and metastasis (12). EGF is a small peptide that participates in cell growth, proliferation, and differentiation. In the tumor environment, releasing EGF by tumor cells causes serum EGF overexpression, which in turn accelerates tumor growth (13). Studies have shown that high EGF expression is correlated with the proliferation, adhesion, invasion and other activities of tumor cells (14). IL-8, a cytokine of the chemotactic factor family, plays an essential role in demic pathological processes and is considered an active factor in inflammatory carcinoma (15). As research has pointed out, IL-8 is highly expressed in the serum and gastric carcinoma tissues of patients with gastric carcinoma and is related to carcinoma occurrence, invasion, and differentiation (16). In this study, serum Livin, EGF, and IL-8 levels of patients decreased postoperatively, with the reduction being much more significant in the case group. A possible reason is that the excision of the lesion blocked the production or release of Livin, EGF, and IL-8 and that the minimum stretch and invasion during endoscopic submucosal dissection allowed fewer amounts of Livin, EGF, and IL-8 to enter the bloodstream.

Operative wounds can be a source of stress that evokes traumatic stress responses, resulting in increased levels of CRP, an acute phase protein (17). It has been reported that 0.4%–5% of patients

undergoing radical surgery for gastric carcinoma develop postoperative gastroplegia, primarily caused by reductions in GAS and MTL levels (18, 19). In this study, serum CRP levels increased, and GAS and MTL levels decreased in both groups postoperatively; however, CRP levels were lower, and GAS and MTL levels were higher in the case group than in the control group. A reasonable explanation for these results is that the operative wounds caused CRP overexpression and intraoperative traction on the gastrointestinal tract, along with stress responses, inhibited the secretion of GAS and MTL. Additionally, the minimum traction and invasion during endoscopic submucosal dissection produced only small stresses, i.e., small increases in CRP levels and minimal impact on the gastrointestinal tract. The reduced suppression of GAS and MTL ensured the protection of stomach function and reduced the risk of gastroplegia.

During the development of gastric carcinoma, overexpressed tumor markers are released into the bloodstream, raising their serum levels (20). Therefore, abnormally increased serum tumor marker levels often indicate the presence and growth of a tumor (21). CA199 and CA724 are vital indicators of the digestive tract malignant tumors and are highly expressed in the serum of patients with gastric carcinoma. Therefore, they can serve as valuable references in the diagnosis and prognosis of gastric carcinoma (22, 23). In addition, MG7-Ag has been recently found to be a specific marker of gastric carcinoma and is expressed more in patients with gastric carcinoma than in those with gastritis (24). In this paper, CA199, CA724, and MG7-Ag levels decreased in both groups postoperatively, with the case group being lower than those in the control group ($P < 0.05$). The reason for this may be that tumor excision cut off the source of serum tumor markers, thereby reducing their serum levels, and compared with traditional laparotomy, minimum invasion ensured by endoscopic submucosal dissection lowered the number of markers entering the bloodstream.

In this study, EORTC QLQ-C30 and EQ-VAS scores one week and three months postoperatively decreased and then increased in both groups compared with preoperative scores. One week after surgery, scores in the case group were higher than those in the control group. These results indicate that patients with early gastric carcinoma had a poor quality of life after surgery and that endoscopic submucosal dissection was beneficial in maintaining a better quality of life. This may be because pain and limited activity after early surgery decrease patients' quality of life and health status, and traditional laparotomy imposes severe trauma and long recovery periods, leading to a significant decrease in the quality of life. In contrast, the minimum trauma and rapid postoperative recovery associated with endoscopic submucosal dissection contribute to better patient quality of life and health. Patients undergoing endoscopic submucosal dissection exhibited a smaller score decline, and their quality of life stabilized postoperatively (25). Over time, the two groups did not show any significant difference in patients' quality of life and health status. In terms of long-term survival and recurrence, there were no differences between the two groups in 3- or 5-year survival or 5-year recurrence rates. The 5-year survival rate in both groups was >90%, consistent with a report by Suzuki et al. (26). These findings indicate that patients undergoing endoscopic submucosal dissection exhibited similar long-term survival and recurrence rates as those undergoing traditional radical surgery.

This study systematically observed the effects of endoscopic submucosal dissection on the postoperative quality of life of patients with early gastric carcinoma, the changes in serum Livin, EGF, and IL-8 before and after surgery, and the effects of traumatic stress on patients, and the efficacy of endoscopic submucosal dissection for early gastric carcinoma was confirmed from the aspect of efficacy, serum cytokine levels, traumatic stress and postoperative quality of life, which was the innovation of this study. However, there are some limitations to this study. It is a single-center study with a small number of patients, which may lead to data bias. Meanwhile, laparoscopic gastrectomy has been widely performed in multilevel hospitals, and this factor was not taken into account at the beginning of the study design, which is a shortcoming of this study, and a control group of laparoscopic surgery patients will be set up for further control study in the next step.

6. Conclusion

In conclusion, endoscopic submucosal dissection in patients with early gastric carcinoma provides the advantages of a short operative time, less perioperative bleeding, rapid postoperative recovery, less traumatic stress and postoperative complications, and reduced serum Livin, EGF, IL-8, and tumor marker levels. The long-term prognosis is not significantly different between patients treated using the two surgical approaches.

Acknowledgments

None.

Footnotes

Conflicts of Interest: None.
Data availability statement: The raw data supporting the conclusions of this article will be made available by the authors without undue

reservation.

Ethics statement: This study was approved by the Beijing First Hospital of Integrated Traditional Chinese and Western Medicine. All patients provided written informed consent.

Author contributions: LX and QD designed the study and performed the experiments, LX collected the data, QD analyzed the data, LX and QD prepared the manuscript. All authors read and approved the final manuscript.

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