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ABOUT COVER

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ORIGINAL ARTICLE

Retrospective Study

Influence of postoperative complications on long-term survival in liver transplant patients

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Abstract

BACKGROUND

Liver transplant (LT) is a complex procedure with frequent postoperative complications. In other surgical procedures such as gastrectomy, esophagectomy or resection of liver metastases, these complications are associated with poorer long-term survival. It is possible this happens in LT but there are not enough data to establish this relationship.

AIM

To analyze the possible influence of postoperative complications on long-term survival and the ability of the comprehensive complication index (CCI) to predict this.

METHODS

Retrospective study in a tertiary-level university hospital. The 164 participants were all patients who received a LT from January 2012 to July 2019. The follow-up was done in the hospital until the end of the study or death. Comorbidity and risk after transplantation were calculated using the Charlson and balance of risk (BAR) scores, respectively. Postoperative complications were graded according to the Clavien-Dindo classification and the CCI. To assess the CCI cut-off value with greater prognostic accuracy a receiver operating characteristic (ROC) curve was built, with calculation of the area under the curve (AUC). Overall survival was estimated according to the Kaplan-Meier test and log-rank test. Groups were compared by the Mann-Whitney test. For the multivariable analysis the Cox regression was used.

RESULTS

The mean follow-up time of the cohort was 37.76 (SD = 24.5) mo. A ROC curve of

dataset available from the corresponding author at juancarlos.rodriguezs@scsalud.es.

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CCI with 5-year survival was built. The AUC was 0.826 (0.730-0.922), $P < 0.001$. The cut-off was calculated by means of the Youden index with a result of 35.95. The sensitivity was 84.6% and the specificity 61.3%. Survival curves for comparison of patients with CCI score < 36 *vs* ≥ 36 were calculated. The estimated 5-year survival was 57.65 and 43.95 months, respectively (log-rank < 0.001). This suggests that patients with more severe complications exhibit worse long-term survival. Other cut-off values were analysed. Comparison between patients with CCI < 33.5 *vs* > 33.5 (33.5 = median CCI value) showed estimated 5-year survival was 57.4 and 45.71 months, respectively (log-rank < 0.0001). Dividing patients according to the mode CCI value (20.9) showed an estimated 5-year survival of 60 mo for a CCI below 20.9 *vs* 57 mo for a CCI above 20.9 (log-rank = 0.147). The univariate analysis did not show any association between individual complications and long-term survival. A multivariate analysis was carried out to analyse the possible influence of CCI, Charlson comorbidity index, BAR and hepatocellular carcinoma on survival. Only the CCI score showed significant influence on long-term survival.

CONCLUSION
A complicated postoperative period – well-defined by means of the CCI score – can influence not only short-term survival, but also long-term survival.

Key words: Liver transplant; Complication; Survival; Comprehensive complication index; Clavien; Prognosis

Core tip: It is not known whether postoperative complications after liver transplant (LT) are associated with poorer long-term survival. The objective of the present study is therefore to analyse the possible influence of postoperative complications on the long-term survival of LT patients. A retrospective study of 164 LT patients was conducted, analysing complications and grading them by means of the Clavien classification and the comprehensive complication index (CCI). We found that a complicated postoperative period – well-defined by means of the CCI score – can influence not only short-term survival, but also long-term survival.

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INTRODUCTION

Liver transplant (LT) is performed in the end stage of a chronic liver disease or acute liver failure. In spite of medical progress –skills and technology- LT is a complex procedure associated with many potential complications, such as bleeding, portal or arterial thrombosis, primary liver dysfunction or biliary leaks or stenosis[1-4]. Many complications require interventional procedures, reoperations, prolonged intensive care unit and hospital stays and some lead to death.

Several studies have investigated the possible influence of these postoperative complications on the long-term survival of patients treated because of gastric cancer[5,6], colo-rectal cancer[7], colo-rectal liver metastases[8], or squamous cell esophageal carcinoma[9]. However, there are no data concerning LT with the exception of papers dealing with graft damage after biliary or ischemic complications[10].

Postoperative complications were graded using the Dindo-Clavien classification[11], which comprises seven grades based on the therapy required to treat each complication. However, this score does not combine multiple complications in the same patient. The comprehensive complication index (CCI)[12] further develops the Dindo-Clavien classification, taking into account all complications to provide each patient with a combined morbidity score.

The objective of the present study is therefore to analyse the possible influence of postoperative complications on the long-term survival of LT patients.

MATERIALS AND METHODS

Study design: Retrospective study in a tertiary university hospital in Santander (Spain). The participants were all the patients who received a LT from January 2012 to July 2019. All were adults (n = 164) and received a cadaveric transplant following donor brain death -153- or cardiac death -11-. A technique of cava preservation with piggy-back anastomosis was performed in every case. Follow-up was done in the hospital until the end of the study or death.

Demographic, clinical, surgical and pathological variables were recorded from hospital data bases.

Comorbidity was calculated using the Charlson index[13]. The risk after transplantation was calculated by means of the balance of risk (BAR) score[14], which includes donor age, recipient age, model for end-stage liver disease (MELD) score, retransplantation, pretransplant life support and cold ischemia time.

Postoperative complications were graded according to the Clavien-Dindo classification[11] -which grades the most severe complication -and the CCI[12], which calculates the sum of all the complications that are weighted for their severity. CCI was calculated according to the formula available at https://www.assessurgery.com/about_cci-calculator/, with a score between 0 –no complications- and 100 –death-.

Statistical analysis

The programme IBM SPSS Statistics version 21.0 (Chicago, EE. UU., 2012) was used. Values of $P < 0.05$ were considered significant. The Kolmogorov–Smirnov test was used to assess the distribution of the continuous variables. To assess the CCI cut-off value with greatest prognostic accuracy a receiver operating characteristic (ROC) curve was built, with calculation of the area under the curve (AUC). The highest Youden index (sensitivity + specificity -1) was calculated.

For survival analysis, patients who died in the postoperative period before discharge from hospital were excluded. Overall survival was estimated according to the Kaplan-Meier test and distribution comparison with the log-rank test. Groups were compared with the Mann-Whitney test.

To investigate whether other factors such as Charlson comorbidity index, BAR score or hepatocellular carcinoma also influenced survival, a multivariable analysis using the Cox regression was performed. The statistical review of the study was performed by a biomedical statistician.

RESULTS

One hundred and sixty-four patients, 130 men (79.3%) and 34 women (20.7%) with a mean age of 55.3 years (SD = 9.5) were analysed. The most frequent indications for transplant were hepatocellular carcinoma (36%) and alcoholic liver disease (26.7%).

The main variables of donor and recipient are shown in Table 1.

All donors were cadaveric, 153 from brain death and 11 from controlled cardiac death (Maastricht type III), with premortem cannulation and normothermic regional perfusion using extracorporeal membrane oxygenation.

Thirteen patients died in hospital (7.9%): 4 due to primary liver dysfunction, 4 due to biliary complications, 3 because of portal thrombosis and 2 because of arterial bleeding.

The most frequent complications (Table 2) were biliary leaks -23.2%-, biliary strictures –9.1%-, wound infection -13.4%- and hepatic artery thrombosis -10.4%-. The treatment consisted of re-transplantation in 6 patients (3.6%) due to ischemic cholangiopathy -2-, hepatic artery thrombosis -2-, hyperacute rejection -1- and portal thrombosis -1-.

The patients were graded according to the Dindo-Clavien classification considering the most severe complications (Table 3).

Hepatic artery thrombosis happened in 17 patients and was treated as follows: Surgical revascularization in 8, anticoagulation or antiaggregation in 7 and retransplantation in the 2 above-mentioned cases. Portal thrombosis happened in 15

Table 1 Donor and recipient features

Recipient variables	
Gender, *n* (%)	
Men	130 (79.3)
Women	34 (20.7)
Child	
A	60 (36.8)
B	65 (39.9)
C	38 (23.3)
Indication, *n* (%)	
OH	43 (26.7)
HPC	58 (36)
VHC	13 (8.1)
Retransplantation	13 (8.1)
Other	34 (20.7)
Age, mean ± SD	55.34 ± 9.55
BMI, mean ± SD	26.34 ± 4.27
Charlson index, mean ± SD	5.96 ± 2.06
MELD, mean ± SD	15.45 ± 6.93
BAR score, mean ± SD	6.14 ± 3.73
CCI score, mean ± SD	42.43 ± 25.01
Donor variables, mean ± SD	
Age	61.59 ± 16.02
Cold ischemia (min)	327.03 ± 119.2
Donor type	
Brain death	93.3%
Cardiac death	6.7%
Death cause cerebrovascular	80%
Trauma	12.7%
Other	7.3%

HPC: Hematopoietic progenitor cell; VHC: Venous hematocrit; BMI: Body mass index; MELD: Model for end-stage liver disease; BAR: Balance of risk; CCI: Comprehensive complication index.

patients and was treated with anticoagulation in 14 and in one by the above-mentioned retransplantation. All patients with biliary leaks or strictures were initially treated by means of endoscopically-placed stents, although one later needed hepatico-jejunostomy.

The mean value of CCI was 4243 (SD = 2501).

Fourteen patients died during follow-up. The causes were: 3 septic complications not directly related with the transplant, 4 biliary complications, 1 bleed due to hepatic artery pseudoaneurism, 2 due to spread of hepatocellular carcinoma, 2 cases of humoral rejection, 1 necrotizing pancreatitis and one death of unknown etiology.

Survival analysis

The mean follow-up time of the cohort was 37.76 (SD = 24.5) mo. A ROC curve of CCI with 5-year survival was built. The AUC was 0.826 (0.730-0.922), $P < 0.001$. The cut-off was calculated by means of the Youden index with a result of 35.95. The sensitivity was 84.6% and the specificity 61.3% (Figure 1, Table 4).

Table 2 Postoperative complications and 5-yr survival, *n* (%)

Complications			5-yr Survival	Log rank
Acute rejection	Yes	10 (6.1)	55.1	0.857
	No	154 (93.3)	55.8	
Arterial thrombosis	Yes	17 (10.4)	48.3	0.057
	No	147 (89.6)	56.5	
Portal thrombosis	Yes	15 (9.1)	51.1	0.722
	No	149 (90.9)	54.5	
Biliary stricture	Yes	15 (9.1)	54.7	0.898
	No	149 (90.9)	55.7	
Biliary leak	Yes	38 (23.2)	55.4	0.574
	No	126 (76.8)	56.9	
Wound infection	Yes	22 (13.4)	55.3	0.568
	No	142 (86.6)	58.8	
Acute renal failure	No	89 (54.3)	58	0.237
	AKIN I	40 (24.4)	52.1	
	AKIN II	18 (11)	53.2	
	AKIN III	17 (10.4)	53.1	
Death	Yes	13 (7.9)		
	No	151 (92.1)		

Survival curves for comparison of patients with CCI scores < 36 *vs* ≥ 36 were calculated. The estimated 5-year survival was 57.65 and 43.95 months, respectively (P < 0.001) (Figure 2A).

Other cut-off values were analysed. Comparison between patients with CCI < 33.5 *vs* > 33.5 (33.5 = median CCI value) showed estimated 5-year survival was 57.4 and 45.71 mo, respectively (P < 0.0001) (Figure 2B). Comparison between patients with CCI < 20.9 *vs* > 20.9 (20.9 = mode CCI value) showed estimated 5-year survival was 60 and 57 months, respectively (P = 0.147) (Figure 2C).

The univariate analysis did not show any association between individual complications and long-term survival (Table 2).

The multivariate analysis to investigate the possible influence of other factors on survival is shown in Table 5. Only the CCI score showed significant influence on long-term survival.

DISCUSSION

Postoperative complications are frequent and often severe after liver transplantation. Many of them lead to intervention, reoperation, retransplantation and even death[15]. The postoperative mortality of the present study was 7.9%, similar to other European series -8-20%-[16,17] and according to the standard of the Spanish Society of LT[18].

Several studies have investigated the possible influence of complications on long-term survival in other abdominal surgical diseases. In colorectal cancer liver metastases, researchers have hypothesized[19,20] that postoperative morbidity prolongs systemic inflammatory response and induces changes that worsen long-term survival as observed in some studies[21,22].

Gastric cancer investigations[5,6] have also observed association between postoperative complications and lower cancer-specific survival. The authors hypothesize that complications could inhibit immune response to spreading tumor cells leading to decreased survival.

Studies in colorectal cancer[7] have found an association between postoperative morbidity due to exclusively infectious complications –mainly severe - and lower long-term survival.

Table 3 Number of complications according to Clavien classification

Clavien	Number	Description (*n*)
0	9 (5.5)	
I	4 (2.4)	Surgical wound hematoma (3)
		Postoperative ileus (1)
II	73 (44.5)	Portal thrombosis (5)
		Vena cava thrombosis (1)
		Intraabdominal hematoma (6)
		Intraabdominal abscess (2)
		Biliary leak (4)
		Surgical wound infection (7)
		Bacteriemia (2)
		Respiratory complication (8)
		Acute renal failure (19)
		Urinary tract infection (4)
		Acute rejection (3)
		Thrombocytopenia (1)
		Neurological alteration (5)
		Fever without a source (5)
		Hypocalcemia (1)
IIIa	22 (13.4)	Intraabdominal abscess (3)
		Biliary leak (12)
		Biliary stricture (6)
		Perforated diverticulitis (1)
IIIb	26 (15.9)	Arterial thrombosis (7)
		Portal thrombosis (2)
		Biliary leak (6)
		Biliary stricture (1)
		Hemoperitoneum (7)
		Vena cava leak (1)
		Abdominal hernia (1)
		Abdominal compartment syndrome (1)
IVa	16 (9.8)	Arterial thrombosis (4)
		Portal thrombosis (1)
		Biliary leak (1)
		Hemoperitoneum (7)
		Vena cava leak (2)
		Primary graft dysfunction (1)
IVb	1 (0.6)	Primary graft dysfunction (1)
V	13 (7.9)	Arterial thrombosis (4)
		Portal thrombosis (2)
		Hemoperitoneum (4)
		Ischemic cholangiopathy (1)

		Biliary stricture (1)	
		Bilateral pneumonia (1)	
Total	164 (100)		

Table 4 Five-year survival according to comprehensive complication index, *n* (%)

CCI		5-yr Survival (mo)	Log-rank
< 20.9	12 (7.3)	60.0	0.167
≥ 20.9	152 (92.7)	50.7	
< 33.5	78 (47.6)	57.4	< 0.001
≥ 33.5	86 (52.4)	45.7	
< 36	88 (53.7)	57.6	< 0.001
≥ 36	76 (46.3)	43.9	

CCI: Comprehensive complication index.

Table 5 Five-year survival multivariable analysis

Variables	*P* value	HR (95%CI)
BAR	0.101	0.922 (0.797-1.016)
Charlson index	0.58	0.764 (0.463-1.007)
CCI	< 0.001	0.941 (0.922-0.96)
HPC	0.311	0.277 (0.028-1.402)

BAR: Balance of risk; CCI: Comprehensive complication index; HPC: Hematopoietic progenitor cell.

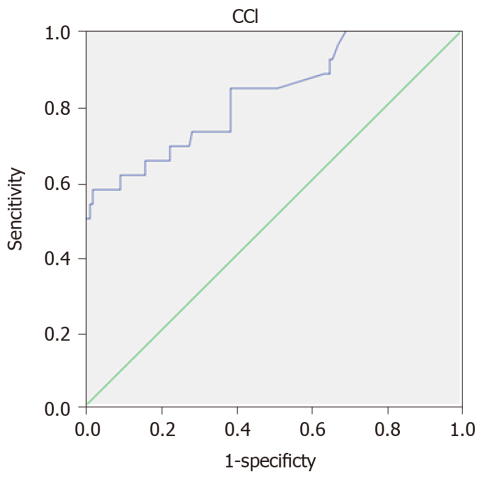

Figure 1 Comprehensive complication index receiver operating characteristic curve and 5-yr survival. CCI: Comprehensive complication index.

The same association has been found with esophageal squamous cell carcinoma, especially with pulmonary complications and anastomotic leaks[9].

However, there is no data concerning LT with the exception of papers dealing with graft damage after biliary or ischemic complications[10].

In this study, LT patients with more postoperative complications –estimated by the CCI score – exhibit a significantly lower survival than patients with fewer complications. No single complication was associated with worse long-term survival, although this could be due to the sample size. Nevertheless, the CCI – as a measure of

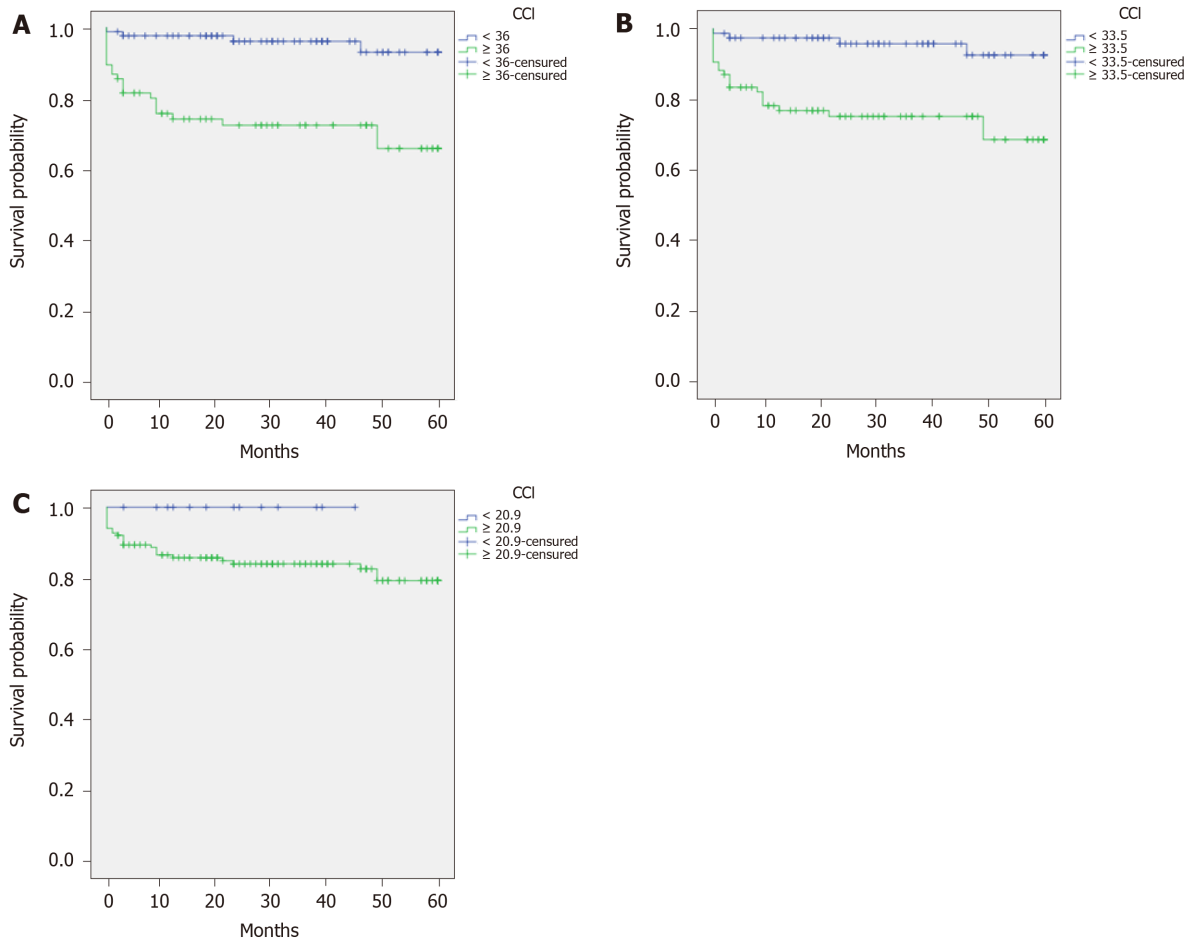

Figure 2 Five-year survival between patients with comprehensive complication indexs. A: Comprehensive complication index (CCI) < 36 *vs* CCI ≥ 36 (P < 0.001); B: CCI < 33.5 *vs* CCI ≥ 33.5 (P < 0.001); C: CCI < 20.9 *vs* CCI ≥ 20.9 (P = 0.147). CCI: Comprehensive complication index.

overall morbidity – was shown to be an independent negative predictive factor of long-term survival.

The multivariable analysis was performed to rule out the influence of other variables on long-term survival. MELD was not included because it was already weighted within the BAR variable. Patients with greater preoperative comorbidity could be expected to suffer more complications after surgery, and therefore to have lower long-term survival. However, we found long-term survival was not influenced by other pre-transplant factors such as the Charlson and BAR scores or the presence of hepatocellular carcinoma. Only the CCI score showed significant influence on long-term survival.

Of note, according to the analysed cut-offs, not many complications are needed to enter in the high-risk zone: Only one complication requiring interventional treatment under general anesthesia or two treated without general anesthesia are enough. As a result, enhancing postoperative care is extremely important not only to minimize postoperative mortality but also to improve long-term survival.

The association between complications and poorer survival is not clear. Many of the delayed deaths were related with surgical aspects such as vascular or biliary problems[23], but they seemed more aggressive in those patients with complications in the immediate postoperative period. The main hypothesis is that an increased and prolonged inflammatory systemic response produces deleterious effects. In addition, these patients receive high doses of immunosuppressive drugs in the immediate postoperative period and prolonged treatment thereafter. The role of this treatment is unknown.

This study has several limitations, such as its retrospective and unicentric design, the relatively small number of patients and the limited follow-up of the patients. Prospective multicentric studies with more patients are needed to validate our results.

In conclusion, according to our results, a complicated postoperative period –well defined by means of the CCI score- can influence not only short-term survival, but also

long-term survival in LT recipients.

ARTICLE HIGHLIGHTS

Research background

In surgical procedures such as gastrectomy, esophagectomy or resection of liver metastases, postoperative complications are associated with poorer long-term survival. It is possible this happens in liver transplant (LT) but there are not enough data to establish this relationship.

Research motivation

To define whether long-term prognosis is influenced by postoperative complications after LT.

Research objectives

To analyze the possible influence of postoperative complications on long-term survival and the ability of the comprehensive complication index (CCI) to predict this.

Research methods

Retrospective study of 164 LT patients. The medical records concerning postoperative complications and long-term survival were analyzed. Univariate and multivariable tests were performed for statistical analysis.

Research results

A ROC curve of CCI with 5-year survival was built. Survival curves for comparison of patients with CCI cut-off values of 36 and 33.5 showed significant statistical differences, suggesting that patients with more severe complications exhibit worse long-term survival. A multivariate analysis was carried out to analyze the possible influence of CCI, Charlson comorbidity index, BAR and hepatocellular carcinoma on survival. Only the CCI score showed significant influence on long-term survival.

Research conclusions

A complicated postoperative period – well-defined by means of the CCI score – can influence not only short-term survival, but also long-term survival of LT patients.

Research perspectives

Refinement and surgical technique and postoperative care are mandatory to improve short-term result but this also influence long-term survival.

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ORIGINAL ARTICLE

Retrospective Study

Easy fixation effects the prevention of Peterson's hernia and Roux stasis syndrome

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Institutional review board statement: This study was retrospective, and no interference with patients' treatment was made. Thus, the approval by the Institutional Review Committee of Juntendo University Hospital was waived.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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Abstract

BACKGROUND

Laparoscopic distal gastrectomy (LDG) for gastric cancer has been progressed and popular in Japan, since it was first described in 1994. Several reconstruction methods can be adopted according to remnant stomach size, and balance of pros and cons. Roux-en-Y (R-Y) reconstruction is a one of standard options after LDG. Its complications include Petersen's hernia and Roux stasis syndrome. Here we report our ingenious attempt, fixation of Roux limb and duodenal stump, for decreasing the development of Petersen's hernia and Roux stasis syndrome.

AIM

To develop a method to decrease the development of Petersen's hernia and Roux stasis syndrome.

METHODS

We performed ante-colic R-Y reconstruction after LDG. After R-Y reconstruction, we fixed Roux limb onto the duodenal stump in a smooth radian. *Via* this small improvement in Roux limb, Roux limb was placed to the right of the ligament of Treitz. This not only changed the anatomy of the Petersen's defect, but it also kept a fluent direction of gastrointestinal anastomosis and avoided a cross-angle after jejunojejunostomy. 31 patients with gastric cancer was performed this technique after R-Y reconstruction. Clinical parameters including clinicopathologic characteristics, perioperative outcomes, postoperative complication and follow-up data were evaluated.

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RESULTS

The operative time was (308.0 ± 84.6 min). This improvement method took about 10 min. Two (6.5%) patients experienced pneumonia and pancreatitis, respectively. No patient required reoperation or readmission. All patients were followed up for at least 3 year, and none of the patients developed postoperative complications related to internal hernia or Roux stasis syndrome.

CONCLUSION

This 10 min technique is a very effective method to decrease the development of Petersen's hernia and Roux stasis syndrome in patients who undergo LDG.

Key words: Laparoscopy distal gastrectomy; Roux-en-Y reconstruction; Internal hernia; Roux limb syndrome; Gastric cancer

Core tip: We developed a method, fixation of Roux limb and duodenal stump. This not only changed the anatomy of the Petersen's defect, but it also kept a fluent direction of gastrointestinal anastomosis and avoided a cross-angle after jejunojejunostomy. None of the patients had complications related to Petersen's hernia and Roux stasis syndrome by at least three years of follow-up in this study. This technique is a simple and effective method to decrease the development of Petersen's hernia and Roux stasis syndrome.

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INTRODUCTION

Since the first laparoscopic distal gastrectomy (LDG) for gastric cancer was reported in Japan, it has been progressed and popular due to the benefits for patients[1]. According to survey from Nationwide Survey of Endoscopic Surgery in Japan, distal gastrectomy was accounted for the most proportion among all the laparoscopic gastrectomy[1,2].

Evidence-based oncological outcomes of LDG for gastric cancer were obtained from many random clinical trials[1,3,4]. After that, more and more attention was attracted to improve patients' quality of life. Digestive tract reconstruction is a critical aspect of the procedure in addition to not only the oncologic goals of disease resection but also the quality of life for patients. Reconstruction methods by laparoscopy have been developed during more than 10 year. An optimal technique of digestive tract reconstruction after distal gastrectomy has not been reached definitive consensus. There are several reconstruction methods of digestive tract after laparoscopic distal gastrectomy including Billroth I, Billroth II, and Roux-en-Y anastomosis. Roux-en-Y gastrojejunostomy is now used worldwide for the prevention of alkaline reflux gastritis, esophagitis, dumping syndrome, and carcinogenesis of the gastric remnant.

A gastrojejunostomy in R-Y reconstruction can be performed through either the retrocolic or the antecolic route. The retrocolic reconstruction is conventionally and commonly performed by open surgery. The antecolic route for R-Y reconstruction is favored especially in the laparoscopic procedure with better exposure to the mesenteric defect and lesser mesenteric defects. However, some complications such as internal hernia are closely related with antecolic route for the reason that jejunojejunostomy and Petersen's defect are created during reconstruction[5].

About 10% to 30% of the patients after R-Y reconstruction suffer from Roux stasis syndrome which consists of abdominal pain, vomiting and post-prandial nausea[6]. The pathogenic mechanisms of Roux stasis syndrome are not completely identified. It has been proposed that the occurrence of Roux stasis syndrome is related to functional obstruction of the Roux limb or interruption of electrical conduction caused by amputation of the jejunum[7]. Many improved anastomosis methods were invented, such as uncut R-Y reconstruction or β-shaped R-Y reconstruction[8,9]. However, some of

them are technically complex elements and time-consuming. Given that surgical technical factors involving the Roux limb play an important role in the development of these two complications, we developed a method of fixation of Roux limb and duodenal stump to narrow the Petersen's defect and decrease the development of Roux stasis syndrome (Figure 1).

In this retrospective study, we describe this simple method and report our experience with 31 successful modified laparoscopic Roux-en-Y gastrojejunostomy with fixation of Roux Limb and duodenal stump evaluate feasibility, safety, and short-term outcomes.

MATERIALS AND METHODS

Patients

Between July 2015 and March 2017, 31 patients with gastric cancer underwent LDG with ante-colic R-Y reconstruction by the same surgeon at the Department of Gastroenterology and Minimally Invasive Surgery at Juntendo University School of Medicine. Clinical parameters included clinicopathologic characteristics, perioperative outcomes, postoperative complication and follow-up data.

Surgical techniques

Patient positioning and placement of the trocars: The patient was placed in the supine position and general anesthesia was induced. A 12 mm trocar was inserted through the umbilical region by the open method, and carbon dioxide pneumoperitoneum was established. The additional four trocars were placed, including two 12 mm trocars in the right and left lower abdomen and two 5mm trocars in the right and left upper abdomen.

Laparoscopic intracorporeal Roux-en-Y gastrojejunostomy after distal gastrectomy: Laparoscopic mobilization of the stomach and lymph node dissection were performed in a conventional manner. The vagus nerve was not preserved. The duodenum was divided distal to the pylorus with an endoscopic linear stapler (Endo-GIA 60-3, Covidien), then the stomach was divided with two endoscopic linear staplers. Usually one-third or one-fifth of the stomach was preserved. The specimen was removed through an extended 4 cm incision in the umbilical port. The jejunum, 20 cm distal to the ligament of Treitz, was prepared for a Roux limb, and the mesentery of this jejunum was divided for a distance of 8 cm. The prepared jejunum then was divided with an endoscopic linear stapler to ensure a tension free-gastrojejunostomy. A side-side jejunojejunostomy was fashioned 30 cm distal to the planed gastrojejunostomy using endoscopic linear staplers under direct vision through the umbilical incision. The jejunojejunostomy defect was closed with nonabsorbable sutures in an intermittent fashion. Pneumoperitoneum was rebuilt and the jejunal limb was brought to the gastric remnant through an ante-colic route. A right-oriented Roux limb was created such that the cut end of the jejunal limb faced the greater curvature of the gastric remnant (Figure 2A). The jejunal limb was anastomosed to the greater curvature of the stomach side-to-side with an endoscopic stapler, then the site of entry for the linear stapler was closed using a running hand sewn suture (Figure 2B).

Surgical technique for fixation of Roux limb and duodenal stump: We summarized the surgical procedures as follows. All the procedures were performed laparoscopically. First, the duodenal stump was laparoscopically buried, with suturing performed by hand. The rows of staples on the duodenal stump may then be reinforced by a continuous absorbable seromuscular barbed suture (*e.g.*, 3-0 V-loc, Covidien), which buries the suture line (Figure 2C). Second, the alimentary was then fixed to the duodenal stump at a location to prevent torsion of the Roux limb (Figure 2D). No intention was made to close the Petersen's defect in any of the patients during the surgery. The final reconstruction is illustrated in Figure 3.

RESULTS

From July 2015 to March 2017, we performed this technique after R-Y reconstruction for gastric cancer in 31 consecutive patients (19 men and 12 women). The characteristics of the patients are shown in Table 1. The mean patient age was 66.2 ± 13.0 years (mean ± SD), and the mean BMI was 21.5 ± 2.7 kg/m^2 (mean ± SD). 2

Table 1 Clinical characteristics of patients

Content	
Sex	
Male	19
Female	12
Age	66.2 ± 13.0
ASA score	
1	29
≥ 2	2
Body mass index (kg/m^2)	21.5 ± 2.7
History of laparotomy	2
Pathological stage	
IA	15 (48.4%)
IB	1 (3.2%)
IIA	2 (6.4%)
IIB	6 (19.4%)
IIIA	6 (19.4%)
IIIB	1 (3.2%)

Number of patients is shown unless otherwise indicated. Values are shown as mean ± SD. Body Mass Index = body weight/height^2 (kg/m^2).

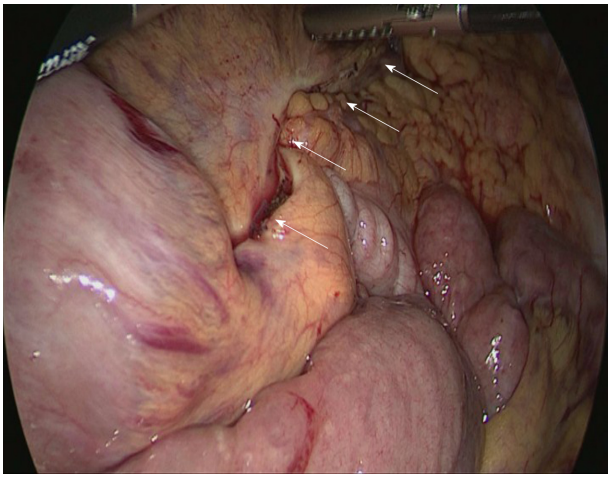

Figure 1 Petersen's defect (white arrow).

patients had a history of laparotomy. Most of the patients (48.4%) had stage IA gastric cancer according to the pathological staging of gastric cancer.

The intraoperative data and postoperative outcomes are summarized in Table 2. The operative time was 308.0 ± 84.6 min (mean ± SD). The fixation time was 10 ± 1.6 min (mean ± SD). The blood loss volume was 70.1 ± 76.0 mL (mean ± SD). The number of lymph nodes harvested was 28.9 ± 4.1 (mean ± SD). After LDG, on average, the patients tolerated liquids on the first day and a soft diet on the second postoperative day. The postoperative hospital stay was 13.5 ± 2 d (mean ± SD).

The postoperative complications are summarized in Table 3. There was no conversion to open surgery in any of the patients. Two patients experienced pneumonia and pancreatitis after surgery, respectively. All patients were discharged with satisfactory recovery and were evaluated postoperatively by routine abdominal computed tomography scan and endoscopy as part of follow-up. The median follow-up period was 44.5 mo (range 37-59 mo). None of the patients had complications

Table 2 Intraoperative data and postoperative outcomes

Content	
Operation time (min)	308.0 ± 84.6
Fixation time (min)	10 ± 1.6
Intraoperative blood loss (mL)	70.1 ± 76.0
Conversion to open surgery, *n* (%)	0 (0)
Extent of lymph node dissection	
≤ D1$^+$	16
D2	15
Number of lymph nodes harvested	28.9 ± 4.1
Clear liquids initiated, median (d)	1
Soft diet initiated, median (d)	2
Postoperative hospital stay (d)	13.5 ± 2

Number of patients is shown unless otherwise indicated. Values are shown as mean ± SD.

Table 3 Postoperative complications

Content	
Anastomotic leak or stenosis	0 (0%)
Anastomotic bleeding	0 (0%)
Roux stasis syndrome	0 (0%)
Internal hernia	0 (0%)
Pancreatitis	1 (3.2%)
Pneumonia	1 (3.2%)
Reoperation, *n* (%)	0 (0%)
Readmission, *n* (%)	0 (0%)

related to internal hernia and Roux stasis syndrome during the follow-up period.

DISCUSSION

Herein we report our method to reduce post-operative Peterson's hernia and Roux stasis syndrome in patients undergoing LDG. There are reports that a laparoscopic approach, non-closure of mesenteric defects, and low BMI are independent risk factors for internal hernia by multivariate analysis[10-13]. One study reported a higher incidence of internal hernia after single-port surgery compared to multi-port surgery, resulting from the relatively difficult manipulation of laparoscopic instruments in single-port surgery[13].

The rate of Petersen's hernia which is a type of internal hernia, with the laparoscopic ante-colic R-Y reconstruction approach without closure of Petersen's defect, was reportedly 2.6% to 4.75% and generally was thought to be higher than with open approach[5,14,15]. One explanation is that laparoscopic surgery is less likely to form adhesions and promotes earlier intestinal peristalsis than laparotomy, which leads to a higher incidence of internal hernia[16]. Although all defects are closed at the time of the initial surgery, internal hernia still occurs in some cases[15,17]. Previous studies speculated that the large decrease in mesenteric fat after distal gastrectomy might lead to the reopening of the defect despite an initially complete suture[18-20]. An early diagnosis of internal hernia is a challenge for most surgeons because of atypical clinical symptoms and lack of sensitive imaging techniques[17]. Furthermore, the internal hernia may be delayed, so it is necessary to develop an effective technique to

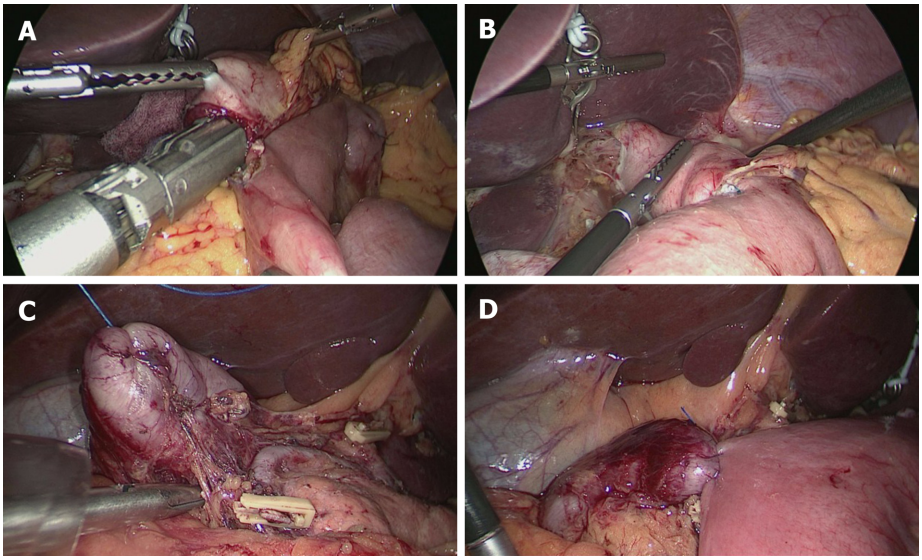

Figure 2 Laparoscopic intracorporeal Roux-en-Y gastrojejunostomy after distal gastrectomy and surgical technique for fixation of Roux limb and duodenal stump. A: The cut end of the jejunal limb faced the greater curvature; B: The site of entry was closed using a running handsewn suture; C: The duodenal stump was embedded with seromuscular suture; and D: Roux limb was fixed on the duodenal stump.

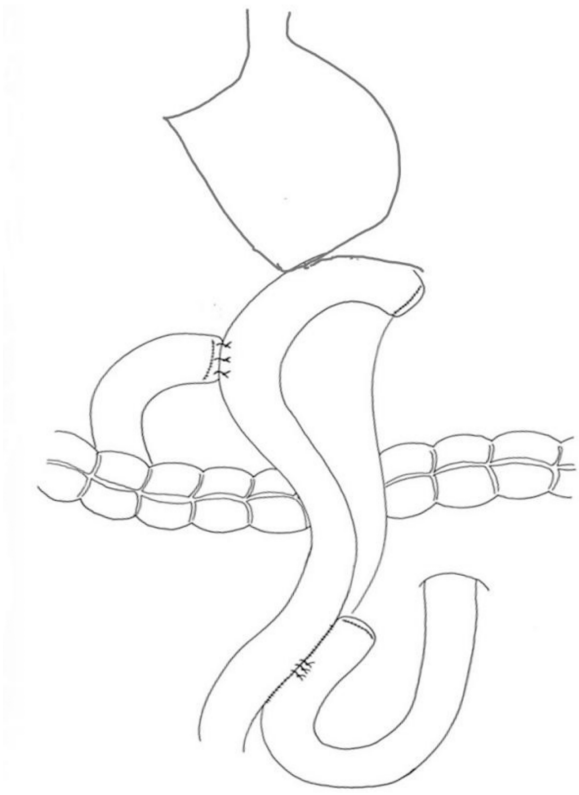

Figure 3 The final reconstruction.

prevent an internal hernia during the surgery.

The boundaries of Petersen's defect are defined as the transverse mesocolon, the mesentery of the Roux limb and the retroperitoneum[21]. Unlike with laparoscopic gastric bypass, subtotal resection of the stomach with lymph node dissection widens the space behind the Roux limb in the ante-colic Roux-Y reconstruction, which may often result in Petersen's hernia. Closure of all the mesenteric defects with non-absorbable suture in a running fashion was considered the most effective method for preventing internal hernia[5,16,22], however, a tight closure of the Petersen's defect from the root of the mesentery of the Roux limb and transverse mesocolon to the transverse

colon is difficult with the laparoscopic view. As reported by Hirahara *et al*[16] one way to minimize the defect is to place the residual greater omentum in the defect between the Roux limb and the transverse mesocolon. Although this technique can prevent Petersen's hernia, it may not be suitable for patients undergoing total resection of the omentum. In our approach to reducing the likelihood of Peterson's hernia, we initially fix Roux limb onto the duodenal stump with a smooth radian and tension, then change the angle of the opening of Petersen's defect and narrow the space behind the Roux limb. This procedure decreases the mobility of Roux limb and makes the mesentery of Roux limb and the transverse mesocolon stick tightly. Thus, this technique eliminates the narrowed Petersen's defect through rapid formation of adhesions behind Roux limb. Compared with the many closure stitches needed to repair Petersen's defect in a relatively poor exposure, our reported procedure does not require mesentery stitches, is time-saving and is simple and effective. Two large retrospective studies of internal hernia reported that the median interval time after gastrectomy for hernia formation was from 15 mo to 20.9 mo[11,13]. None of the patients developed internal hernias by at least three years of follow-up in this study. To some extent, the follow-up data supports our small change about Roux limb in surgical technique.

In addition, surgical technical factors with Roux limb have been taken into account for the cause of Roux stasis syndrome. Gowen[23] speculated that one of the causes for Roux stasis syndrome is partial obstruction near or at the gastrointestinal anastomosis, but without stomal stenosis. This author analyzed the types of partial obstruction and found that they were related to postoperative adhesions or a kinked loop around the gastrointestinal anastomosis as a result of non-standard surgical techniques. Masui *et al*[6] also suggested that the adhesion between Roux limb and the suture of the gastric remnant, which was produced a strong bend of Roux limb to the lesser curvature of gastric remnant, could be a cause of Roux stasis syndrome. To prevent this, we fix Roux limb onto the duodenal stump with appropriate tension, which ensures a fluent direction of the gastrointestinal anastomosis by avoiding the angle after the gastroenterostomy. Moreover, through this technique the alimentary limb lies to the right of the ligament of Treitz and does not cross the proximal jejunum (biliopancreatic limb), which allows digestive juices and food to pass smoothly into the distal small intestine.

In conclusion, here we report a case series of a simple and effective method for decreasing the development of Petersen's hernia and Roux stasis syndrome following R-Y reconstruction. Although Petersen's hernia is a rare complication of R-Y reconstruction, it is difficult to diagnose and may cause serious postoperative complications that require additional surgery and may even result in death[11,13]. Roux stasis syndrome is also widely reported and results in poor post-operative nutritional status[24-26]. Furthermore, with our described technique, no patients had complications related to internal hernia and Roux stasis syndrome. This technique is a simple and effective method to decrease the incidence of internal hernia and Roux stasis syndrome. There are some limitations in our study. Its retrospective nature may induce some bias. Because of the length of follow up, our study did not provide enough data to show conclusions about long-term outcomes.

ARTICLE HIGHLIGHTS

Research background

Roux-en-Y reconstruction has been one of the standard options after laparoscopic distal gastrectomy. Its complications include Petersen's hernia and Roux stasis syndrome. Although Petersen's hernia is a rare complication, it is difficult to diagnose and cause serious postoperative complications. Meanwhile, Roux stasis syndrome is widely reported and reduces the post-operative nutritional status of patients.

Research motivation

Many improved methods were invented for decreasing the incidence of Petersen's hernia and Roux stasis syndrome, however, some of them are technically complex elements and time-consuming. We developed an easy and effective method to narrow the Petersen's defect and reduce the development of Roux stasis syndrome using surgical techniques.

Research objectives

The primary objective of the study was to develop an easy and effective method to

decrease the development of Petersen's hernia and Roux stasis syndrome.

Research methods

We fixed Roux limb onto the duodenal stump in a smooth radian after Roux-en-Y reconstruction. *Via* this small improvement in Roux limb, Roux limb was placed to the right of the ligament of Treitz. This not only changed the anatomy of the Petersen's defect, but it also kept a fluent direction of gastrointestinal retrospective analysis review of the data of 31 consecutive patients who was performed this technique between July 2015 and March 2017.

Research results

This improvement method took about 10 min. All patients were followed up for at least 3 year, and none of the patients developed postoperative complications related to internal hernia or Roux stasis syndrome.

Research conclusions

This 10 min technique is a very effective method to decrease the development of Petersen's hernia and Roux stasis syndrome in patients who undergo laparoscopic distal gastrectomy

Research perspectives

In this study, we report a case series of a simple and effective method for decreasing the development of Petersen's hernia and Roux stasis syndrome. Because of the length of follow up, our study did not provide enough data to show conclusions about long-term outcomes. We will continue to perform this technique and collect more data to prove the long-term effect of this technique.

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ORIGINAL ARTICLE

Observational Study

Drug-eluting beads transarterial chemoembolization sequentially combined with radiofrequency ablation in the treatment of untreated and recurrent hepatocellular carcinoma

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Abstract

BACKGROUND

Drug-eluting beads transarterial chemoem-bolization (DEB-TACE) has the advantages of slow and steady release, high local concentration, and low incidence of adverse drug reactions compared to the traditional TACE. DEB-TACE combined with sequentially ultrasound-guided radiofrequency ablation (RFA) therapy has strong anti-cancer effects and little side effects, but there are fewer related long-term studies until now.

AIM

To explore the outcome of DEB-TACE sequentially combined with RFA for patients with primary hepatocellular carcinoma (HCC).

METHODS

Seventy-six patients with primary HCC who underwent DEB-TACE sequentially combined with RFA were recruited. Forty patients with untreated HCC were

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included in Group A, and 36 patients with recurrent HCC were included in Group B. In addition, 40 patients with untreated HCC who were treated with hepatectomy were included in Group C. The serological examination, preoperative magnetic resonance imaging examination, and post-treatment computed tomography enhanced examination were performed for all patients. The efficacy was graded as complete remission (CR), partial remission (PR), stable disease and progressive disease at the 3rd, 6th, and 9th. All patients were followed up for 3 years and their overall survival (OS), disease-free survival (DFS) were assessed.

RESULTS

The efficacy of Group A and Group C was similar ($P > 0.05$), but the alanine aminotransferase, aspartate aminotransferase and total bilirubin of Group A were lower than those of Group C (all $P < 0.05$). The proportions of CR (32.5%), PR (37.5%) were slightly higher than Group A (CR: 27.5%, PR: 35%), but the difference was not statistically significant ($\chi^2 = 0.701$, $P = 0.873$). No operational-related deaths occurred in Group A and Group C. The OS (97.5%, 84.7%, and 66.1%) and the DFS (75.0%, 51.7%, and 35.4%) of Group A at the 1st, 2nd, and 3rd year after treatment were similar with those of Group C (OS: 90.0%, 79.7%, and 63.8%; DFS: 80.0%, 59.7%, and 48.6%; $P > 0.05$). The OS rates in Group A and Group B (90%, 82.3%, and 66.4%) were similar ($P > 0.05$). The DFS rates in Group B (50%, 31.6%, and 17.2%) were lower than that of Group A ($P = 0.013$).

CONCLUSION

The efficacy of DEA-TACE combined with RFA for untreated HCC is similar with hepatectomy. Patients with recurrent HCC could get a longer survival time through the combined treatment.

Key words: Drug-eluting beads transarterial chemoembolization; Ultrasound; Radiofrequency ablation; Hepatocellular carcinoma; Untreated; Recurrent

Core tip: Drug-eluting beads transarterial chemoembolization (DEB-TACE) can continuously and slowly release chemotherapeutic drugs compared to traditional TACE. It can maintain higher local concentrations meanwhile reducing the adverse drug reactions. DEB-TACE combined with ultrasound-guided radiofrequency ablation (RFA) has a strong anti-cancer effect, but due to its expensive price, there are fewer clinical studies. This study explored the outcome of DEA-TACE combined with RFA in the treatment of primary and recurrent hepatocellular carcinoma (HCC). The results indicated that the outcome of combined treatment for untreated HCC was comparable to hepatectomy, with less bleeding, faster recovery, and less damage to liver function. More importantly, the combination therapy has a positive effect on the treatment of recurrent HCC with fewer complications and can prolong the survival time of patients.

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INTRODUCTION

Ultrasound-guided radiofrequency ablation (RFA) is one of the most effective treatments for primary hepatocellular carcinoma (HCC)[1]. However, due to the limitation of local tumor control range, RFA is difficult to completely cover tumors with a diameter of more than 3 cm[2]. The combined use of transarterial chemoembolization (TACE)[3-5] and RFA is one of the strategies to obtain a larger ablation

coverage volume[6-8]. Nevertheless, some concentrated chemotherapy drugs are easily to release into the peripheral blood after TACE, which will result in some adverse reactions (*e.g.* liver injury)[9]. Drug-eluting beads TACE (DEB-TACE) is a new treatment method for replacing traditional embolic agents with drug-loaded microspheres[10]. Because of its good deformability, the microsphere can adhere to the blood vessel to achieve complete embolization, and avoid aggregation at the proximal or distal end of the blood vessel[11-14]. Zhang *et al*[15] found through the animal experiments that DEB-TACE can slowly release chemotherapy drugs and achieve a long-term blood drug concentration with less liver injury. Clinically, Yamakado *et al*[16] found that DEB-TACE combined with RFA is more effective in controlling tumor development for patients with liver metastases from colon cancer. The post-treatment efficacy and safety are better than traditional TACE combined with RFA. However, due to the high cost of drug-loaded microspheres, there are limited reports of DEB-TACE combined with RFA in patients with primary HCC. The aim of this study is to explore the possible benefits of DEB-TACE sequentially combined with ultrasound-guided RFA by analyzing the liver function and clinical efficacy of patients with untreated and recurrent HCC.

MATERIALS AND METHODS

Research participants

From March 2014 to March 2016, patients with primary HCC who underwent DEB-TACE sequentially combined with RFA were recruited. Forty patients with untreated HCC were included in Group A, while 36 patients with recurrent HCC were included in Group B. Besides, another 40 patients with untreated HCC who were treated with hepatectomy were included in Group C with a 1:1 match using a propensity score matching (PSM) (Figure 1). The inclusion criteria of primary HCC were as follows: (1) Age 18-75 years; (2) Diagnosis of primary HCC according to the medical guidelines[17,18]; (3) Invasion of large blood vessel branches and extrahepatic metastases found in imaging examination; (4) Maximum diameter ≤ 7 cm for single tumor, maximum diameter ≤ 3 cm and tumor number ≤ 3 for multiple tumors; and (5) Child-Pugh grade A or B. The exclusion criteria were as follows: (1) Severe coagulopathy; (2) Combined liver decompensation symptoms such as refractory ascites, esophageal varices bleeding or hepatic encephalopathy; and (3) Allergic to contrast agents or chemotherapy drugs. All patients or their families signed an informed consent before treatment, and the study was approved by the ethics committee of Hwa Mei Hospital, University of Chinese Academy of Sciences.

Serological examination

Fasting elbow vein blood was collected from all participants. The separated serum was divided into 2 portions, one for alpha-fetoprotein (AFP) levels (Microparticle Enzyme Immunoassay AxSYM Abbott) and the other for liver function determination such as serum albumin (ALB), serum total bilirubin (TBIL), serum alanine aminotransferase (ALT), and serum aspartate Aminotransferase (AST) by an autoanalyzer (ADVIA® 2400 Clinical Chemistry System, Siemens, Tarrytown, NY). In the measurement process, the relevant operational specifications and quality requirements were strictly followed to ensure the measurement results.

Imaging examination

Preoperative magnetic resonance imaging (MRI) examination: Plain and enhanced scans of the upper abdomen were performed using a Siemens 1.5T superconducting MRI system (Siemens Healthcare, Erlangen, Germany). Conventional acquisition of axial T1-weighted image (T1WI) (Figure 2A) and T2-weighted image (T2WI) (Figure 2B) were required. The contrast agent was gadolinium-diethylene-triamine penta-acetic acid (Gd-DTPA) at a dose of 0.1 mmol/kg and an injection rate of 4 ml/s. The dynamic enhanced scan images of the hepatic arterial phase (Figure 2C), portal vein phase (Figure 2D), and parenchymal phase (Figure 2E) were obtained

Post-treatment computed tomography (CT) enhanced examination: A CT-enhanced scan was performed using a Siemens SOMATOM Difinition 64-segment dual-source spiral CT scanner (Siemens, Germany). The patient was fasted for 6-8 h before the examination, and the supine position was taken. The nonionic contrast agent iohexol (General Electric Healthcare, Waukesha, Wisconsin, USA) with 0.9% sodium chloride injection was injected. A dynamic contrast-enhanced CT scan of the upper abdomen

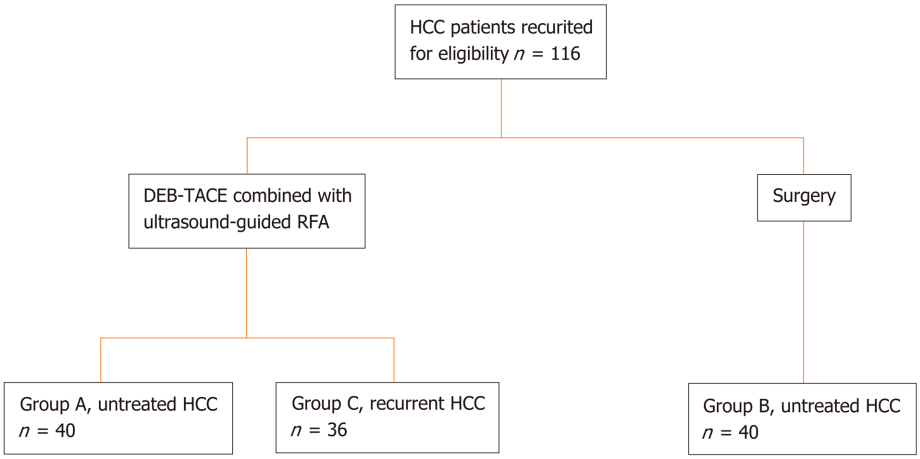

Figure 1 Flow diagram of patient grouping. DEB-TACE: Drug-eluting beads transarterial chemoem-bolization; HCC: Hepatocellular carcinoma; RFA: Radiofrequency ablation.

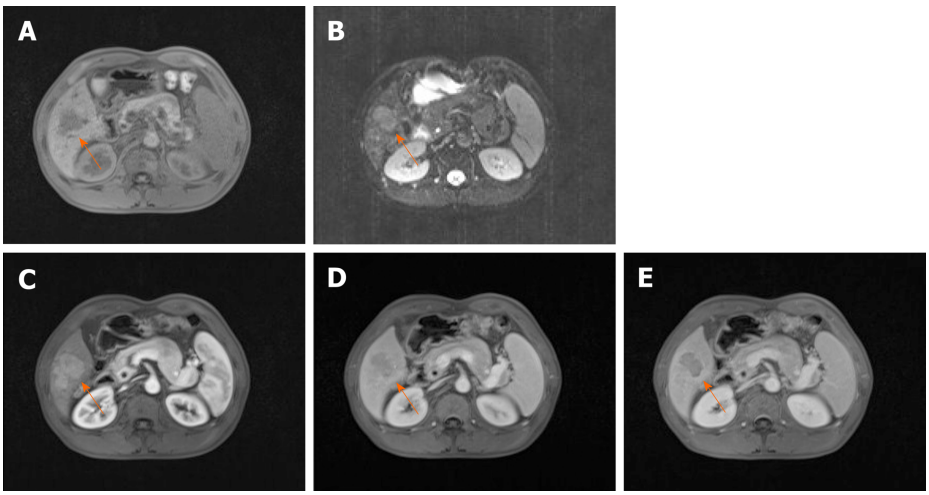

Figure 2 Preoperative magnetic resonance imaging plain and enhanced scans of the upper abdomen. The location of liver tumor in each figure was marked by the arrow. A: T1-weighted image; B: T2-weighted image; C: Enhanced scan of hepatic arterial phase; D: Enhanced scan of hepatic portal vein phase; E: Enhanced scan of hepatic parenchymal phase.

was performed and the dynamic enhanced examinations of hepatic arterial phase (Figure 3A), portal vein phase (Figure 3B), and parenchymal phase (Figure 3C) were obtained.

Treatment protocol

DEB-TACE sequentially combined with RFA: Patients in Group A and group B received DEB-TACE sequentially combined with RFA treatment. The Allura X-per FD20 digital substraction angiography (Philips Medical Systems, Madison, WI, USA) was used to perform hepatic angiography to determine the location, shape, size, and number of tumors, and then to select the tumor-feeding arteries. Epirubicin was loaded into 100-300 um of CalliSpheres drug-loaded microspheres (Heng Rui Galison, Suzhou, China) for TACE. The injection was continued until the contrast flow rate was very slow. The embolization results were confirmed by angiography, and the vascular sheath and catheter were withdrawn after the satisfied embolization (Figure 4).

After DEB-TACE, was performed for 1-2 wk, and RFA was performed after the liver function recovered. RFA was performed using a 17-gauge internally cooled electrode (Cool-TipTM, Valleylab, Boulder, CO, USA) under the guidance of ALOKA Prosound Alpha 7 ultrasound system (Hitachi AlokaMedical Systems, Tokyo, Japan). The electrode needle was punctured into the tumor nodule, and the needle was placed according to the location and size of the tumor. The ablation range covered the entire cancerous foci and the surrounding 0.5-1 cm of liver tissue. When the ablation was

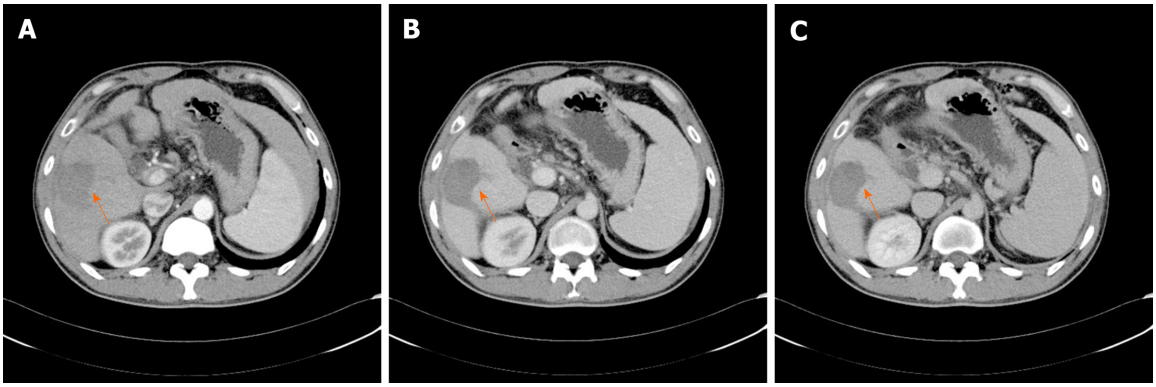

Figure 3 Post-treatment computed tomography enhanced examination of the upper abdomen. The location of liver tumor in each figure was marked by the arrow. A: Enhanced scan of hepatic arterial phase; B: Enhanced scan of hepatic portal vein phase; C: Enhanced scan of hepatic parenchymal phase.

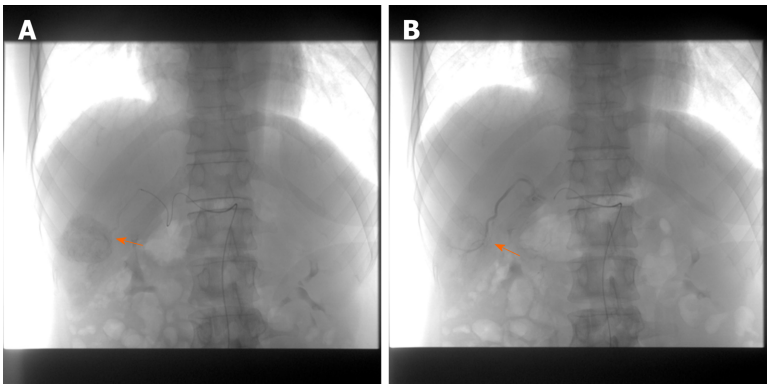

Figure 4 The drug-eluting beads transarterial chemoembolization process of hepatocellular carcinoma. The location of liver tumor in each figure was marked by the arrow. A: Tumor shown in hepatic arteriography before drug-eluting beads transarterial chemoembolization (DEB-TACE); B: Tumor disappeared in hepatic arteriography after DEB-TACE.

started, the needle tip gradually warmed up and maintained for 6-12 min after reaching the target temperature (105°C). After the ablation was completed, the ablation apparatus was set to the needle channel ablation mode, and then gradually retracted (Figure 5).

Hepatectomy: Hepatectomy was performed for patients in Group C after observing the size, number, location, and surrounding organs in detail. After the operation was completed, the bleeding at the surgical incision site was carefully observed and the abdominal cavity was closed layer by layer.

Liver protection treatment: All groups were given diammonium glycyrrhizin enteric-coated capsules or tiopronin liver-protective therapy, and lamivudine or adefovir dipivoxil were administered orally for more than 6 mo.

Post-treatment evaluation of short-term and long-term efficacy

Liver function tests were performed at the 1st week and 1st month after treatment to assess liver damage. The enhanced CT was scanned at the 3rd, 6th, and 9th month after treatment and the efficacy was graded according to modified response evaluation criteria in solid tumors[19] [complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD)]. All patients who participated in the study were followed up for 3 years, and serum AFP levels and liver CT were reviewed every 3 month. The endpoint event was defined as tumor recurrence, local tumor progression (enlarged foci on contrast-enhanced CT images around the ablated tumor), distant metastasis, and death. The patient's refusal to visit and the exit is defined as loss to follow-up. Overall survival (OS) and disease-free survival (DFS) were calculated 3 years after treatment.

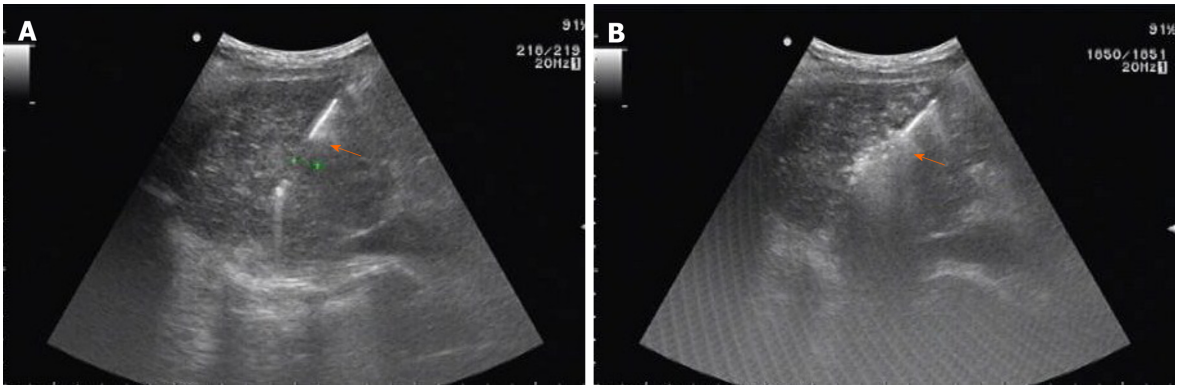

Figure 5 The process of ultrasound-guided radiofrequency ablation after drug-eluting beads transarterial chemoembolization. The location of liver tumor in each figure was marked by the arrow. A: Needle placement during radiofrequency ablation (RFA); B: Ablation during RFA.

Statistical analysis

The statistical analysis was performed using SPSS (Chicago, IL, USA) software (version 22.0). PSM was used to avoid the effects of selective bias and confounding factors on treatment outcomes[20]. Age, tumor size, number of tumors, Child-Pugh classification, AFP and liver function indicators were used as covariates. A logistic regression model was included to estimate the probability of the subjects being assigned to Group A and Group C, and then individuals with similar probabilities were enrolled from the two groups for pairing to achieve randomization criteria. In this study, Group A and Group C were matched by 1:1, and the caliper value was 0.2. The numerical data were expressed as mean ± SD and *t*-test was used for the comparison between the two groups. The categorical variables were expressed as number and percentage and the comparison between the two groups was performed by the χ^2 test. The Kaplan Meier curve was used to analyze the prognosis of the patient. Statistical significance was defined as 2-tailed $P < 0.05$ for all tests.

RESULTS

Comparison of the baseline data between Group A and Group C

Comparison of baseline data between Group A and Group C is shown in Table 1. The gender, age, tumor size, number of tumors, Child-Pugh classification, AFP and liver function indexes were similar in the two groups. The differences were not statistically significant (all $P > 0.05$).

Comparison of the clinical efficacy between Group A and Group C

At the 3rd month after treatment, in the patients of Group A, the number of CR was 11 (27.5%), PR was 14 (35%), and the treatment efficiency was 62.5%. In the patients of Group C, the number of CR was 13 (32.5%), PR was 15 (37.5%), and the treatment efficiency was 70%. It was slightly higher than Group A, but the difference was not statistically significant ($\chi^2 = 0.701$, $P = 0.873$). At the 6th and 9th month after treatment, the SD of the two groups decreased slightly, and the PD increased. However, the clinical efficacy between the two groups was still similar, and the differences were not statistically significant (both $P > 0.05$, Table 2).

Comparison of the liver function between Group A and Group C

Transient liver damage occurred in both groups at the 1st week after treatment. Among them, patients in Group A had lower ALT, AST and TBiL compared with Group C (all $P < 0.05$, Table 3). Liver function-related indicators were improved in both groups at the 1st month after treatment.

Analysis of post-treatment complications in Group A and Group C

In Group A, 14 patients started to have fever at the 2nd or 3rd day after treatment, and 4 of them had a body temperature of more than 38.5 °C. They were given anti-infective and antipyretic treatments, and improved in 3-5 d. Eleven patients had different degrees of post-embolic syndrome, 10 patients hepatic pain, 18 patients elevated transaminase, and 3 patients had ascites. All of them were effectively relieved after

Table 1 Comparison of baseline clinical data between Group A and Group C

	Group A (n = 40)	Group C (n = 40)	t/χ^2 value	P value
Gender (Male)	29	31	0.267	0.606
Age (yr)	62.82 ± 12.93	61.38 ± 10.29	0.551	0.583
Tumor size (cm)	3.75 ± 1.21	3.68 ± 1.17	0.263	0.793
Number of tumors			0.050	0.823
Single	22	21		
2-3	18	19		
Child-Pugh classification			0.054	0.816
A	26	25		
B	14	15		
TBiL (μmol/L)	18.28 ± 5.28	17.83 ± 5.16	0.583	0.562
AFP (ng/ml)	612.29 ± 127.38	625.93 ± 139.27	0.457	0.649
ALB (g/L)	37.19 ± 5.39	36.93 ± 5.33	0.217	0.829
ALT (U/L)	35.27 ± 15.14	36.42 ± 17.46	0.315	0.754
AST (U/L)	38.63 ± 15.13	40.41 ± 16.52	0.503	0.617

AFP: Alpha-fetoprotein; ALB: Serum albumin; ALT: Aminotransferase; AST: Aspartate aminotransferase; TBiL: Total bilirubin.

Table 2 Comparison of the efficacy between Group A and Group C at the 3rd, 6th, and 9th month after treatment, n (%)

	3nd month		6th month		9th month	
	Group A	Group C	Group A	Group C	Group A	Group C
CR	11 (27.5)	13 (32.5)	11 (27.5)	13 (32.5)	11 (27.5)	13 (32.5)
PR	14 (35.0)	15 (37.5)	14 (35.0)	15 (37.5)	14 (35.0)	15 (37.5)
SD	13 (32.5)	11 (27.5)	12 (30.0)	10 (25.0)	10 (25.0)	10 (25.0)
PD	2 (5.0)	1 (2.5)	3 (7.5)	2 (5.0)	4 (10.0)	2 (5.0)
Efficiency	25 (62.5)	28 (70.0)	25 (62.5)	28 (70.0)	25 (62.5)	28 (70.0)
χ^2 value	0.701		0.583		0.855	
P value	0.873		0.900		0.836	

CR: Complete remission; PR: Partial remission; PD: Progressive disease; SD: Stable disease.

symptomatic treatment and liver protection treatment for one week. Serious complications such as needle-free transfer, peripheral organ damage, and biliary fistula were not found. In Group C, 21 patients developed infection, including 11 wound infections, 6 pulmonary infections, and 4 intestinal infections. Six patients developed ascites. They were effectively relieved after the corresponding anti-infective treatment and liver protection treatment. No operational-related deaths occurred in Group A and Group C.

Long-term efficacy of Group A and Group C

Two patients in Group A were lost to follow-up. The average follow-up time was 30.9 ± 1.5 mo. The OS rates at the 1st, 2nd, and 3rd year after treatment was 97.5%, 84.7%, and 66.1%, respectively. The DFS rates were 75.0%, 51.7%, and 35.4%. A total of 13 patients died, including 6 cases of liver failure, 4 cases of hepatorenal syndrome, and 3 cases of upper gastrointestinal bleeding. In Group C, 3 patients were lost to follow-up. The average follow-up time was 32.3 ± 1.2 mo. The OS rates were 90.0%, 79.7%, and 63.8%, and the DFS rates were 80.0%, 59, 7%, and 48.6%. A total of 14 patients died, including 8 patients with liver failure, 5 patients with hepatorenal syndrome, and 1 patient with

Table 3 Comparison of liver function in Group A and Group C at the 1st week after treatment

	Group A	Group C	t/χ^2 value	*P* value
ALB (g/L)	32.82 ± 5.93	31.32 ± 5.28	1.195	0.236
ALT (U/L)	48.29 ± 15.39	67.29 ± 22.93	4.351	0.000
AST (U/L)	51.73 ± 14.92	79.28 ± 20.28	6.921	0.000
TBiL (μmol/L)	23.93 ± 8.38	31.39 ± 9.29	3.771	0.000

ALB: Serum albumin; ALT: Aminotransferase; AST: Aspartate aminotransferase; TBiL: Total bilirubin.

upper gastrointestinal bleeding. Kaplan-Meier survival analysis revealed that the OS and DFS were similar between the two groups, and the differences were not statistically significant (OS: Log Rank = 0.121, $P = 0.728$; DFS: Log Rank = 1.042, $P = 0.307$; Figure 6).

Comparison of the baseline data between Group A and Group B

The tumor size of Group B was less than Group A ($P < 0.05$). The gender, age, number of tumors, Child-Pugh classification, AFP and liver function indexes were similar in the two groups. The differences were not statistically significant (all $P > 0.05$, Table 4).

Long-term efficacy of Group A and Group B

Two patients in Group B were lost to follow-up. The average follow-up time was 31.2 ± 1.4 mo. The OS rates at the 1st, 2nd, and 3rd year after treatment was 90%, 82.3%, and 66.4%, respectively. The OS rates in Group A and Group B were similar, and the difference was not statistically significant (Log Rank = 0.017, $P = 0.897$). The DFS rates were 50%, 31.6%, and 17.2%, respectively, which was lower than that of Group A (Log Rank = 6.123, $P = 0.013$, Figure 7). A total of 13 patients died, including 8 patients with liver failure and 5 patients with hepatorenal syndrome.

DISCUSSION

Due to the hidden onset of HCC, only 30% of patients have the chance of hepatectomy[21]. The treatment after recurrence is also a major problem since the recurrence rate of HCC is higher[22]. Ultrasound-guided RFA is widely used as an effective minimally invasive interventional treatment[23]. It is simple, reproducible, and has few serious post-treatment complications[24]. However, since most RF needles can only ablate 4-5 cm spherical necrosis areas, the ablation effect is satisfied only if the tumor diameter is less than 3 cm. The difficulty of RFA will be significantly increased if the tumor diameter increases, and multiple needles and points must be required for complete ablation[25]. Mazzaferro *et al*[26] indicated that the advantages of hepatectomy over RFA are mainly focus on tumors with a diameter of 3-5 cm. This is because RFA is more likely to leave local tumor lesions during tumor ablation of 3-5 cm in diameter.

TACE before RFA can effectively reduce the residual of active tissue after RFA[27]. The study by Kim *et al*[28] revealed that when RFA combined with TACE was used in the treatment of HCC with a maximum diameter of 3-5 cm, the local tumor progression rate was significantly lower than that of RFA alone. Iezzi *et al*[29] reported that for patients with HCC > 3 cm, the long-term survival of RFA combined with TACE was better than that of TACE or RFA alone. It is worth noting that the traditional emulsion has poor stability, and the chemotherapeutic drugs are easily diffused into the patient's peripheral circulatory system, resulting in an uncontrolled local release of the drug, and easily reducing the local treatment effect and aggravating the systemic adverse reactions of the chemotherapeutic drugs[30].

The development of DEB-TACE solves these two problems[31]. Compared with traditional TACE embolic material (lipiodol), DEB-TACE has the advantage of sustained and slow release. After the drug-loaded microspheres enter the nourishing artery, the loaded drug can be released for up to two weeks, which allows it to maintain a high local concentration in tumor cells and prolong the effect of chemotherapy drugs on tumor cells[32]. In addition, the good deformation ability of the drug-loaded microsphere makes it possible to adhere to the blood vessels to achieve a complete embolization. Meanwhile, the accumulation of chemotherapeutic drugs at

Table 4 Comparison of baseline clinical data between Group A and Group B

	Group A (n = 40)	Group B (n = 36)	t/χ^2 value	P value
Gender (Male)	29	26	0.001	0.978
Age (yr)	62.82 ± 12.93	64.82 ± 11.82	0.722	0.472
Tumor size (cm)	3.75 ± 1.21	3.13 ± 0.82	2.683	0.009
Number of tumors			0.002	0.961
Single	22			
2-3	18	16		
Child-Pugh classification			0.023	0.878
A	26	24		
B	14	12		
TBiL (μmol/L)	18.28 ± 5.28	17.38 ± 5.62	0.738	0.463
AFP (ng/ml)	612.29 ± 127.38	567.28 ± 92.39	1.746	0.085
ALB (g/L)	37.19 ± 5.39	34.94 ± 4.53	1.958	0.054
ALT (U/L)	35.27 ± 15.14	36.49 ± 12.31	0.383	0.703
AST (U/L)	38.63 ± 15.13	36.22 ± 13.26	0.735	0.465

AFP: Alpha-fetoprotein; ALB: Serum albumin; ALT: Aminotransferase; AST: Aspartate aminotransferase; TBiL: Total bilirubin.

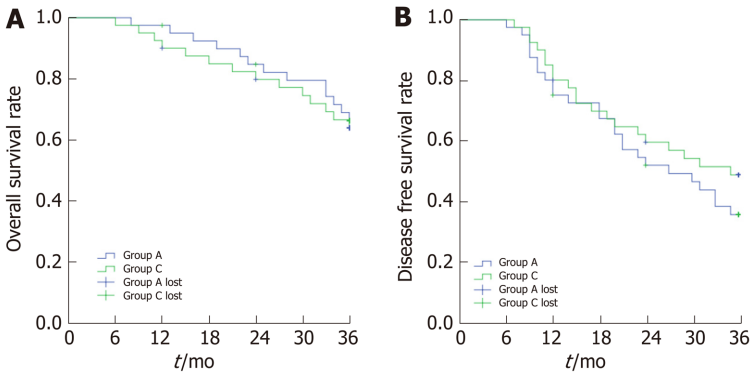

Figure 6 Kaplan-Meier survival analysis of overall survival and disease-free survival of Group A and Group C. A: Overall survival rate analysis. The difference of Group A and Group C was not statistically significant (Log Rank = 0.121, P = 0.728); B: Disease-free survival rate analysis. The difference of Group A and Group C was not statistically significant (Log Rank = 1.042, P = 0.307).

the proximal or distal end of the blood vessel is avoided, reducing the incidence of adverse drug reactions[33-35]. Moreover, the drug dose carried by the microspheres is much larger than that of lipiodol, so DEB-TACE can reach higher chemotherapeutic drug concentrations in tumor tissues, while ensuring lower concentrations in the systemic circulation[36]. Compared with traditional TACE, DEB-TACE has higher disease control rate and overall survival rate[37]. The study by Xiang *et al*[38] reported that DEB-TACE treatment does not aggravate liver toxicity in patients compared to traditional TACE treatment. Song *et al*[39] found that DEB-TACE had less common adverse reactions than traditional TACE. They indicated that HCC patients have better tolerance to DEB-TACE treatment.

Studies have shown that the synergistic effect of DEB-TACE and RFA has a powerful anti-cancer effect[40]. It is demonstrated by the studies of patients with liver metastases from colorectal cancer from Lee *et al*[41] and Ahmed *et al*[42]. Ahmed *et al*[43] found that RFA can increase the permeability of capillaries by dilating the nutritional blood vessels of the tumor, which is conducive to the residual chemotherapy drugs acting on tumor tissue. Zhu *et al*[44] found that the combined application of DEB-TACE and RFA improved the efficacy and survival time. However, combined treatment will increase the cost and prolong the hospital stay. Therefore, there are fewer long-term

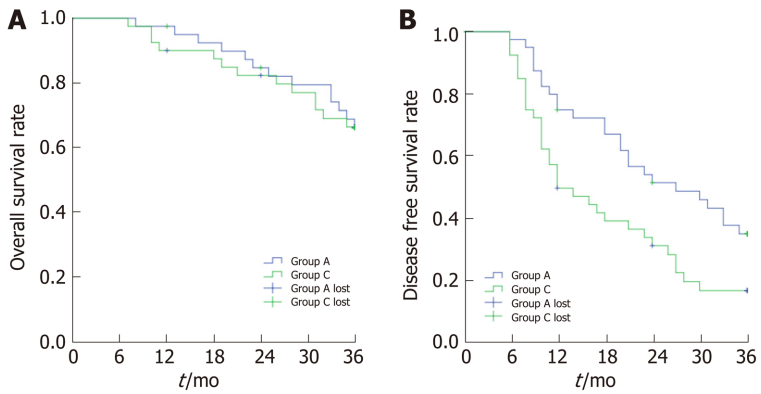

Figure 7 Kaplan-Meier survival analysis of overall survival and disease-free survival of Group A and Group B. A: Overall survival rate analysis. The difference of Group A and Group B was not statistically significant (Log Rank = 0.017, P = 0.897); B: Disease-free survival (DFS rate analysis). The DFS rate of Group B was lower than that of Group A (Log Rank = 6.123, P = 0.013).

studies on DEB-TACE combined with RFA in the treatment of HCC, and its advantages need to be verified by prospective studies. In this study, the long-term follow-up of HCC patients who received the combination of DEB-TACE and RFA was performed to explore the application value of the combined treatment of DEB-TACE and RFA.

Comparison of DEB-TACE combined with RFA and surgical treatment

This study showed that the effective rates of Group A with DEB-TACE combined with RFA and Group C with surgery were similar at the 3rd, 6th, and 9th month. It indicated that DEB-TACE combined with RFA can achieve the same short-term effects as surgical treatment. In terms of liver damage, the results implied that the treatment of DEA-TACE combined with RFA had less damage to the liver than surgical treatment, which is similar to the results of the Pan *et al*[45]. In terms of complications, it indicated that patients treated with DEB-TACE combined with RFA showed better tolerance.

In terms of long-term efficacy, the treatment of DEB-TACE combined with ultrasound-guided RFA can achieve long-term effects similar to surgical treatment. It is worth noting that the average tumor diameter of Group A was 3.75 ± 1.21 cm, of which 16 patients had a tumor diameter > 3 cm. It revealed that the long-term effect of DEB-TACE combined with RFA on > 3 cm tumors is no different from the curative effect of surgical treatment, thus overcoming the limitation of RFA treatment on the tumor volume.

After comparing the short-term and long-term effects of the two groups, we believe that DEB-TACE combined with RFA is safe for patients. Compared with surgery, combined treatment has less trauma, less liver damage, faster post-treatment recovery, and is more suitable for patients with multiple HCC or cirrhosis. In addition, in clinical practice, we found that if the tumor is located around the liver, it is easy to be surgically removed, while RFA is not suitable because it needs to prevent puncture to cause tumor rupture and prevent normal tissues around burns. However, if the tumor is located in the center of the liver parenchyma, RFA has more advantages. Surgical resection requires more normal tissues to be sacrificed and it is easy to cause cancer cell metastasis due to surgical compression.

DEB-TACE combined with ultrasound-guided RFA in the treatment of untreated and recurrent HCC

HCC recurrence is the main factor limiting the effectiveness of HCC treatment. Although reoperation is the preferred treatment for recurrent HCC, there are fewer opportunities for reoperation due to surgical adhesions, liver dysfunction, and insufficient residual liver capacity[46,47]. Therefore, DEB-TACE combined with ultrasound-guided RFA is expected to be an effective treatment for patients with recurrent HCC. This study compared the clinical characteristics of patients with untreated and recurrent HCC and found that the clinical characteristics of patients with untreated and recurrent HCC were similar. However, the tumor diameter of patients with recurrent HCC was smaller than that of patients with untreated HCC. It is because HCC patients would be followed up after treatment. Recurrent patients will be detected early by imaging. In terms of long-term efficacy, 13 patients with recurrent

HCC died, and their DFS in 1-3 years was lower than that in patients with untreated HCC. The reason why untreated HCC is more likely to recur than untreated HCC may be because liver volume decreases and liver reserve decreases after liver cancer resection. However, it is worth noting that this study found the OS of recurrent HCC patients in 1-3 years was similar to that of untreated HCC patients, and the difference was not statistically significant. It indicated that in the treatment of recurrent HCC, TACE combined with RFA could well control local tumors and prolong the survival time of patients, and can obtain the same effect as reoperation.

In conclusion, DEB-TACE combined with ultrasound-guided RFA provides a new method for the treatment of HCC. Its short-term effect is comparable to traditional surgical treatment, and it has less bleeding, quicker recovery during treatment, and less damage to liver function. More importantly, DEB-TACE combined with ultrasound-guided RFA in the treatment of recurrent HCC can prolong the survival time of patients. However, this study is still a single-center study, and the sample size is limited. It is necessary to conduct a further study of a larger sample.

ARTICLE HIGHLIGHTS

Research background

Ultrasound-guided radiofrequency ablation (RFA) is one of the most effective treatments for early hepatocellular carcinoma (HCC). However, due to the limitation of local tumor control ability, RFA is difficult to completely cover tumors with a diameter of more than 3 cm. Transarterial chemoembolization (TACE) can significantly reduce the volume of hepatic carcinoma. Hence the combined use of TACE and RFA can obtain a larger ablation coverage volume.

Research motivation

Drug-eluting beads TACE (DEB-TACE) has the advantages of sustained slow release, maintaining a high local concentration, and reducing the incidence of adverse drug reactions compared to traditional TACE. DEB-TACE combined with ultrasound-guided RFA therapy has strong anti-cancer effects and little side effects, but there are fewer related long-term studies in clinical setting.

Research objectives

The aim of our study was to explore the possible benefits of DEB-TACE combined with RFA by analyzing the liver function and clinical efficacy of patients with primary HCC. It is hopeful to help the management of HCC.

Research methods

Seventy-six patients with primary HCC who underwent DEB-TACE combined with ultrasound-guided RFA were recruited. Among them, 40 patients with untreated HCC were defined as Group A, 36 patients with recurrent HCC were defined as Group B, and 40 patients with untreated HCC who were treated with surgery were defined as Group C. All patients underwent serological examination and recorded alpha-fetoprotein and liver function. Liver function tests were performed at the 1st week and 1st month after treatment to assess liver damage. Efficacy was assessed at the 3rd, 6th, and 9th month after treatment. All patients were followed up for 3 years and their overall survival (OS), disease-free survival (DFS) were calculated.

Research results

After 3 mo of treatment, the effective rate of Group A and C was similar. Among them, group A has less damage to liver function during treatment. The OS and DFS were similar in the two groups. It indicated that the efficacy of DEA-TACE combined with ultrasound-guided RFA in the treatment of primary HCC is comparable to traditional surgical treatment. It has faster recovery, and less damage to liver function during treatment. The OS of Group B were similar to Group A, and the DFS of Group B were lower than Group A. It indicated that the efficacy of DEA-TACE combined with ultrasound-guided RFA in the treatment of recurrent HCC is positive, with fewer complications, and it can prolong the survival time.

Research conclusions

The efficacy of DEA-TACE combined with ultrasound-guided RFA in the treatment of primary HCC is comparable to that of traditional surgical treatment. Moreover, it has

less bleeding, faster recovery, and less damage to liver function during treatment. Its efficacy in the treatment of recurrent HCC is positive, with fewer complications, and it can prolong the survival time of patients.

Research perspectives

DEB-TACE combined with ultrasound-guided RFA in the treatment of recurrent HCC has a positive effect, fewer complications, and can prolong the survival time of patients. However, this study is still a single-center study, and the sample size is limited. This study will perform a larger sample and more detailed research with big data services to get more accurate conclusions.

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REVIEW

Gastrointestinal obstruction secondary to enteral nutrition bezoar: A case report

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Abstract

BACKGROUND

Post-operative enteral nutrition *via* gastric or jejunal feeding tubes is a common and standard practice in managing the critically ill or post-surgical patient. It has its own set of complications, including obstruction, abscess formation, necrosis, and pancreatitis. We present here a case of small bowel obstruction caused by enteral nutrition bezoar. It is the second recorded incidence of this complication after pancreaticoduodenectomy in the medical literature.

CASE SUMMARY

The 70-year-old female presented to our institution for a pancreaticoduodenectomy (Whipple's procedure) for pancreatic adenocarcinoma. On day 5 post-operative, having failed to progress and developing symptoms of small bowel obstruction, she underwent a computed tomography scan, which showed features of mechanical small bowel obstruction. Following this, she underwent an emergency laparotomy and small bowel decompression. The recovery was long and protracted but, ultimately, she was discharged home. A literature search of reports from 1966-2020 was conducted in the MEDLINE database. We identified eight articles describing a total of 14 cases of small bowel obstruction secondary to enteral feed bezoar. Of those 14 cases, all but 4 occurred after upper gastrointestinal surgery; all but 1 case required further surgical intervention for deteriorating clinical picture. The postulated causes for this include pH changes, a reduction in pancreatic enzymes and gastric motility, and the use of opioid medication.

CONCLUSION

Enteral feed bezoar is a complication of enteral feeding. Despite rare incidence, it can cause significant morbidity and potential mortality.

Key words: Upper gastrointestinal surgery; Enteral nutrition; Gastrointestinal obstruction; Bezoar; Hepatobiliary; Case report

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Core tip: Enteral feed bezoar is a complication of enteral feeding in the post-operative or critically ill patient. We present the second case in the literature of small bowel obstruction due to enteral nutrition solidification after pancreaticoduodenectomy. Although incidence is rare, it can have significant morbidity and potential mortality. Eight articles summarize 14 cases in the medical literature. Due to a combination of vague symptoms and vulnerable patient cohort, it can have extensive morbidity, with 13/14 cases requiring a second laparotomy. High clinical suspicion and low threshold for return to theatre is advised for these deteriorating patients.

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INTRODUCTION

Post-operative enteral nutrition (EN) *via* gastric or jejunal feeding tubes is a common and standard practice in managing the critically ill patient or post-operative surgical patient with functioning small bowel[1]. It is preferred over total parenteral nutrition (TPN), as it prevents mucosal atrophy and bacterial translocation while preserving intestinal integrity. However, EN it associated with the following complications: Aspiration, malposition, re-feeding syndrome, and solidification. Although rare, solidification of EN brings with it its own set of serious complications, including small bowel obstruction, necrosis, mural abscesses, perforation and pancreatitis[2]. Specifically, small bowel obstruction secondary to EN bezoar has been recorded only 14 times, much less than oesophageal or gastric bezoar, which have been reported 45 times[3]. The vast majority of the literature states that treatment is an emergency laparotomy and decompression and potentially a bowel resection, depending on the operative findings.

CASE PRESENTATION

Chief complaints

The 70-year-old female was electively admitted to our institution for an open pancreaticoduodenectomy for the treatment pancreatic adenocarcinoma. The patient had the chief complaint of painless jaundice.

History of present illness

The jaundice had arisen insidiously over a 6-mo period. It was associated with weight loss and poor appetite. Extensive investigations had been performed, including computed tomography of the chest, abdomen and pelvis, magnetic resonance cholangiopancreatography, endoscopic ultrasound, endoscopic retrograde cholangiopancreatography, and positive emission topography scan. She had also had a diagnostic laparoscopy.

History of past illness

The patient's only past medical history included an open appendectomy for appendicitis.

Physical and imaging examinations and management

As per unit and hospital protocol, immediately post-operation, the patient was admitted to the intensive care unit (ICU) with nasojejunal (NJ) feeding tube. EN commenced 6 h post-operation at 30 mL/h. She required no vasopressor support and on day 1 had the feed rate increased. She was transferred to the surgical ward and the only concern in the immediate post-operative period was high nasogastric (NG) output. This initially improved, and slowly oral intake was introduced. She was

prescribed an osmotic laxative at this time.

On day 5, the patient developed nausea and vomiting, with increasing pain in her central abdomen. Clinically, she had a mild tachycardia and central abdominal tenderness. The initial differential diagnosis of the presentation was postoperative anastomotic leak, particularly supported by the sudden deterioration in clinical picture and timing of the deterioration. Other differentials included postoperative collection and small bowel obstruction, potentially caused by internal hernia. To investigate, a computed tomography was organized; the finding was a large volume of fluid in distal thoracic esophagus and stomach. The tip of the NJ feeding tube was located appropriately within the efferent small bowel loop. There were also features of proximal to mid small bowel obstruction with faecalisation (Figure 1). The transition point was not clearly defined (Figure 2). Adhesions were postulated as a possible cause.

FINAL DIAGNOSIS

Small bowel obstruction caused by EN solidification.

TREATMENT

According to the patient's imaging findings, a laparotomy was performed. Intra-operatively, her small bowel distension had caused multiple serosal tears. One of these was full thickness, causing faecal and feed contamination of the peritoneum (Figure 3). She underwent decompression of her small bowel, extensive washout and enterotomy repair. The anaesthetic team replaced her NJ feeding tube with a standard large bore NG tube, and a central venous catheter was placed to facilitate the commencement of TPN. The patient had a second admission to the ICU for inotropic support and worsening acute kidney injury. Antifungal treatment was added to her existing antibiotic regimen.

The patient's post-operative recovery was slow, with wound dehiscence and intra-abdominal collection; the latter was managed with percutaneously inserted drains. She resumed oral intake on day 15 post-laparotomy and continued on nourishing fluids until discharge. Her wound dehiscence required regular dressing changes and then negative-pressure wound therapy.

OUTCOME AND FOLLOW-UP

The patient was discharged to home on day 37 post-admission. Upon return home, she attended follow-up in the outpatient clinic. She has reported no ongoing issues since her discharge and has resumed full diet. A timeline of her care is outlined in Figure 4.

DISCUSSION

EN is a tried and tested method for the administration of cost-effective complete nutrition in the post-operative surgical patient, having been shown in the literature to reduce post-operative morbidity and mortality[3-5]. EN is favourable over TPN for the reasons previously outlined; it also has greater cost effectiveness and lower complication rate. Further, it is mostly well tolerated by the overall patient population[4-6]. Critically ill patients and those mechanically ventilated represent another cohort of patients that benefit from EN.

The two main routes of administration for EN are gastric and jejunal. EN administration to the small bowel distal to the pylorus has been shown in seven separate randomised control trials to reduce aspiration and regurgitation of feed and to maximise time between administration and absorption. As reported, there is no statistical difference in associated morbidity and mortality rates[7]. The main forms of EN administration to the jejunum are NJ feeding tube and a feeding jejunostomy tube. Both have their advantages and disadvantages, depending on the clinical situation. NJ tubes, in particular, are considered a temporary option, while feeding jejunostomy tubes have their own set of complications, as highlighted by Kitagawa *et al*[8] in 2019,

Figure 1 Computed tomography scan (coronal plane) showing small bowel dilatation and faecalisation. The tip of the nasojejunal feeding tube was located appropriately within the efferent small bowel loop. There were also features of proximal to mid small bowel obstruction with faecalisation.

Figure 2 Computed tomography scan (axial plane) showing dilatation of the small bowel with faecalisation. The transition point was not clearly defined Adhesions were postulated as a possible cause.

where 17 of 100 patients suffered from small bowel obstruction secondary to malrotation related to the feeding tubes.

We performed a literature search of reports from 1966-2020 in the MEDLINE database. The following key words were entered: Gastrointestinal obstruction, EN, solidification, and bezoar. We identified eight articles describing a total of 14 cases of small bowel obstruction secondary to enteral feed bezoar. Among those 14 cases, all but 4 occurred after upper gastrointestinal surgery and most had an admission to an ICU. All but 1 case required further surgical intervention for deteriorating clinical picture. It is important to note that these publications are limited to case reports that are all retrospective; however, the themes, diagnosis and treatments are very similar throughout the published articles.

The first recorded incidence of enteral feed bezoar was published by O'Malley *et al*[9] in 1981. The authors described a single case report of a patient who had had a hemigastrecotmy, vagotomy and Bilroth II procedure to treat a bleeding ulcer. The patient had been receiving his EN through a jejunostomy. He required a second laparotomy for per rectal bleeding and fever, and was noted to have a 75 cm portion of small bowel with inspissated feed. He required resection and was discharged on day 13. It was postulated that intestinal dysmotility and opioid analgesia was the cause of this episode.

In 1990, McIvor *et al*[4] first suggested feed composition as a factor in enteral feed bezoar. Their case report described a patient with thrombotic thrombocytopenic purpura with hospital-acquired pneumonia. The patient was undergoing NG feeding, when on day 8 the patient was diagnosed with Ogilvie's syndrome and underwent colonoscopic decompression. However, without improvement at 2 d later, they

Figure 3 Intra-operative photography of intestinal decompression through an enterotomy, with evidence of enteral feed solidification. These was full thickness, causing faecal and feed contamination of the peritoneum.

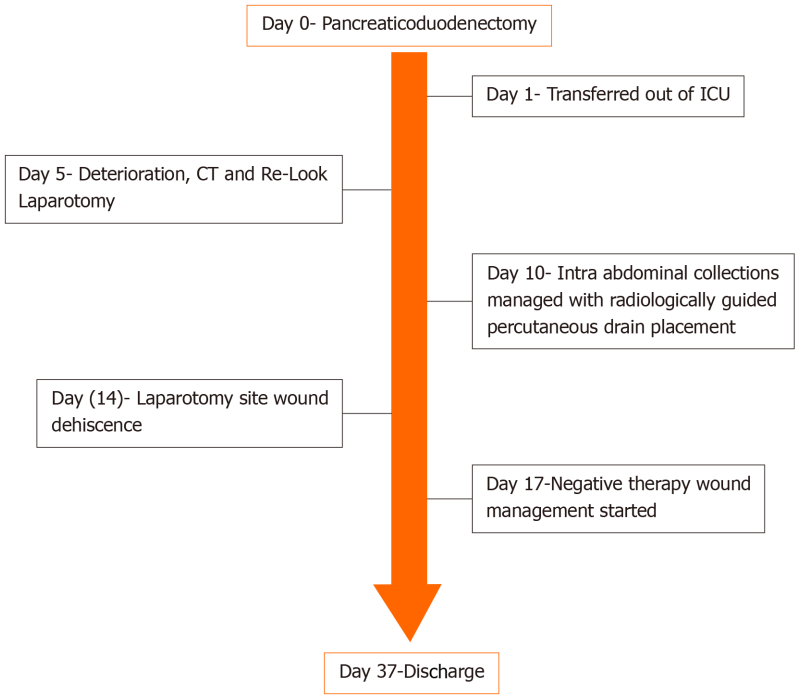

Figure 4 Timeline of case events. ICU: Intensive care unit.

proceeded to laparotomy. Intraoperatively, a caecal bezoar was discovered. It had caused pressure necrosis and avulsion of the caecal pedicle, with the small bowel full of EN. The authors also hypothesized intestinal dysmotility, opioid medication and fibre bulk as causes for this episode.

In 1996, O'Neil *et al*[10] described the first and only non-operatively managed enteral feed bezoar. Their patient was 7 d out from a radical gastrectomy, when he developed high NG output volumes. Results from a barium meal were consistent with small bowel obstruction. Treatment with papain and normal saline was administered through the NG tube, along with intravenous hydration and bowel rest. Further contrast studies showed regression, and the patient was discharged on day 14.

After that, in 1999, Scaife *et al*[5] published a case series of 4 patients. It is notable that none of these patients had undergone gastrointestinal surgery. All 4 were patients who were admitted to the ICU after extensive burns and required NJ feeding after intubation. All 4 had presented with abdominal symptoms at approximately 2 wk into the admission. All had perforation of either small bowel or colon and inspissated feed throughout the gastrointestinal tract. Two of these patients had pressure necrosis injuries secondary to the bezoar.

In 2005, Halkic *et al*[1] reported a case of small bowel obstruction and perforation that occurred at 7 d after a pancreaticoduodenectomy. Intra-operatively, there was impacted enteral feed, with wall necrosis and perforation. The authors likened the causative factors to necrotizing enterocolitis, with hyperosmolarity, bacterial overgrowth and impaction of feed causing mucosal injury. This would have been directly complicated by local vessel vasospasm, ending in necrosis.

The next case series was published by Dedes *et al*[6] in 2006. The authors reported 3 cases after upper gastrointestinal operations. All were given EN in the post-operative period. In addition, all required a second laparotomy to address a mechanical obstruction secondary to the feed solidification. The authors hypothesized that the lack of stomach caused pH disturbance in the remaining gastrointestinal tract. That, along with opioid medication, may have allowed the fibre to precipitate out, causing a plug.

Bouwyn *et al*[11] next described a single case of enteral feed bezoar in 2011. Their case was a patient who had been intubated for pneumonia. However, his NG feed was interrupted on three separate occasions and replaced with TPN. At 6 wk after admission, the patient required a laparotomy for abdominal distension. Intra-operatively, there were sigmoid and small bowel perforations, faecal peritonitis, and multiple gastric and small bowel bezoars. The period of hospitalization to discharge was 4 mo. This case was the first reported in the literature of disseminated EN bezoar. The authors theorized that post-operative paralytic ileus in conjunction with opioid medication was the cause.

Finally, in 2018, Leonello *et al*[2] published a case report of 2 patients with this condition. Both had undergone upper gastrointestinal surgery during their admission and required a second laparotomy to address perforation. The obstruction and perforation were caused by EN solidification. The authors had proposed that neurohormonal changes due to the original surgery and use of bulking agents were the cause.

A summary of these 14 cases and their findings are provided in Table 1.

There are many postulated causes for this complication. Overall, these can be categorized into mechanical and systemic causes. The mechanical causes include anatomical changes, use of bulking agents, and EN composition. Anatomical changes resulting from gastric surgery are known to lead to neurohormonal function and pH changes[1,3,5,11], and such has been suggested to slow gastrointestinal transit and reduce absorption and digestion. With pancreatectomies, the surgery causes a reduction in pancreatic enzymes. Finally, in truncal vagotomies, the reduction in gastric motility and progression is thought to reduce small intestine digestion[4,6,9]. The use of bulking agents and the EN composition have both been indicated in the pathological thickening and solidification of EN[4].

Systemic causes include splanchnic hypoperfusion, dehydration, and pharmacological interventions. Splanchnic hypoperfusion is the most common, occurring either from reduced cardiac output or vasopressor use. It causes a reduction in gastric motility and reduced bicarbonate production[1,2]. Dehydration leads to reduced gastrointestinal tract secretions and a differing composition of EN. Ultimately, it causes pathological thickening.

Pharmacological interventions include sucralfate, morphine and its analogues, and finally medications that interfere with gastrointestinal tract pH (*i.e.* H2 receptor blockers, antacids). Sucralfates bind to the EN, causing insoluble complexes that in turn cause solidification[1,2]. Morphine analogues reduce gastrointestinal tract motility, thereby increasing the likelihood of pathological thickening[1-3,6].

Surgical management is the mainstay of treatment for intestinal and colonic bezoar. All but 1 patient in the literature required operative intervention in the form of a laparotomy. Surgical management itself has been shown to reduce morbidity and mortality[4]. Most patients have had their EN stopped and TPN commenced. This contrasts with oesophageal bezoar, which has been managed both medically and endoscopically. The findings at the time of surgery have been perforation and obstruction. Of note, this has been consistent across the literature. In the majority of cases, the EN showed thickening and in 2 cases, the feed appeared to have become a cast in the bowel[6,11].

It is interesting to note that our case had similarities with the others in the literature. Our patient had undergone a pancreaticoduodenectomy. As we have previously mentioned, this is the second such occurrence published. Thus, a potential cause was the reduction in pancreatic enzymes[1]. Also, she had been in the ICU and initially had been prescribed a morphine analogue and bulking agents. All of the above have been previously postulated as causes for this condition[2,4]. Most likely, there is no single cause and our case represents a multifactorial nature for the cause of bezoar formation.

Table 1 Available literature on enteral nutrition obstruction

Ref.	Year	Patient characteristics				Type of bezoar	Proposed mechanism	Outcome
		Diagnosis on admission/surgery type, if any	Feeding tube location	Bezoar location	Treatment			
O'Malley *et al*[9]	1981	Bleeding ulcer/hemigastrectomy	Jejunum	Small bowel	Resection	Impacted feed	Opioid analgesia Intestinal dysmotility	D/C
McIvor *et al*[4]	1990	TTP	Stomach	Caecum	Resection	Impacted feed	Opioid analgesia; intestinal dysmotility; fibre bulk	D/C
O'Neil *et al*[10]	1996	Gastric cancer Radical gastrectomy	Jejunum	Small bowel	Papain	Unknown	Opioid analgesia (causing paralytic Ileus)	D/C
Scaife *et al*[5]	1999	Burns	Jejunum	Small Bowel/Caecum	Resection	Impacted feed	Bulking agents	D/C
Halkic *et al*[1]	2005	Pancreatic cancer Whipple's procedure	Jejunum	Small bowel	Resection	Impacted feed	Hyperosmolarity; bacterial overgrowth	
Dedes *et al*[6]	2006	Gastric cancer Total gastrectomy	Stomach/jejunum	Small bowel	Enterotomy	Impacted feed	pH disturbance with no stomach, precipitation of fibres	D/C
Bouwyn *et al*[11]	2011	Pneumonia	Stomach	Small bowel	Resection	Multiple small bezoars	Opioid medication (causing paralytic ileus)	D/C
Leonello *et al*[2]	2018	Gastric/intestinal cancer UGI bleeding	Jejunum	Small bowel	Resection	Impacted feed	Neurohormonal changes; bulking agents	Death

D/C: Discharged to home; TTP: Thrombotic thrombocytopenic purpura; UGI: Upper gastrointestinal.

CONCLUSION

Enteral feed bezoar is an uncommon but life-threatening complication of enteral feeding. It can occur in the post-operative surgical patient and critically ill ICU patient. The majority of these patients present with vague abdominal symptoms, deteriorating to septic shock. The management of this condition is usually an exploratory laparotomy and removal of thickened feed. Bowel resection is also required to address necrotic bowel. Operative findings commonly include thickened or inspissated feed, perforation, and necrosis. Given the nature of the presentation, a high clinical suspicion and low threshold for return to theatre is advised. This is especially relevant in the deteriorating patient, to reduce the chance of bowel resection.

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