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EDITORIAL

Perioperative risk factors in patients with liver disease undergoing non-hepatic surgery

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Abstract

The patients with liver disease present for various surgical interventions. Surgery may lead to complications in a significant proportion of these patients. These complications may result in considerable morbidity and mortality. Preoperative assessment can predict survival to some extent in patients with liver disease undergoing surgical procedures. A review of literature suggests nature and the type of surgery in these patients determines the peri-operative morbidity and mortality. Optimization of premorbid factors may help to reduce perioperative mortality and morbidity. The purpose of this review is to discuss the effect of liver disease on perioperative outcome; to understand various risk scoring systems and their prognostic significance; to delineate different preoperative variables implicated in postoperative complications and morbidity; to establish the effect of nature and type of surgery on postoperative outcome in patients with liver disease and to discuss optimal anaesthesia strategy in patients with liver disease.

PERIOPERATIVE RISK FACTORS IN PATIENTS WITH LIVER DISEASE UNDERGOING NON-HEPATIC SURGERY

The number of patients with liver disease presenting for various surgical interventions are increasing. But there are appreciable risk factors which are present perioperatively when these patients undergo surgery under anaesthesia. Careful preoperative assessment and risk stratification in these patients is therefore of paramount importance. The effect of nature and type of surgery on perioperative morbidity and mortality is also important. The purpose of this review is to (1) discuss the effect of liver disease on perioperative outcome; (2) understand various risk scoring systems and their prognostic significance; (3) delineate different preoperative variables implicated in postoperative complications and morbidity; (4) establish the effect of nature and type of surgery on postoperative outcome in patients with liver disease; and (5) discuss optimal anaesthesia strategy in patients with liver disease.

SPECTRUM OF LIVER DISEASE

Fatty liver and non-alcoholic fatty liver disease

Nonalcoholic fatty liver disease is one of the most common cause of chronic liver disease worldwide. The rising prevalence rate is because of increasing epidemic of obesity and metabolic syndrome. Risk of developing postoperative complications or death is more postoperatively after hepatic resection if > 30% hepatocytes are affected with steatosis. However < 30% steatosis is not associated with significantly increased risk of mortality[1].

Obstructive jaundice

Retrospective analysis of 373 patients with obstructive jaundice identified three risk factors for perioperative death: low hematocrit (< 30%), an elevated serum bilirubin (> 11 mg/dL), and a malignant cause of biliary obstruction. The mortality rate was 60% when all three were present whereas it was only 5% when none were present[2]. Hypoalbuminemia, azotemia, and cholangitis were also thought to increase the risk of death. These factors reflect the degree of biliary obstruction[3]. Longstanding biliary obstruction can lead to biliary cirrhosis, which may then influence the outcome of surgery. The reported mortality rate in patients with secondary biliary cirrhosis is 13% within 30 d of surgery[4]. In patients with acute cholangitis and choledocholithiasis, endoscopic decompression of the obstructed bile duct, in combination with intravenous antibiotics, is associated with lower morbidity and mortality than surgical decompression[4].

Acute hepatitis

Most literature regarding surgery in acute hepatitis is very old when laparotomy was part of diagnostic evaluation of patients with icterus[2,5]. Major elective surgery for a patient with suspected acute viral and alcoholic hepatitis should be deferred until the patient has recovered, the exception being life-saving emergency surgery.

Acute liver failure

Patients with acute liver failure (development of jaundice, coagulopathy and hepatic encephalopathy within 26 wk in a patient with acute liver injury in absence of pre-existing liver disease) are critically ill and any surgery other than liver transplantation is contraindicated[4].

Chronic hepatitis

Elective surgery has been reported to be safe in patients with chronic mild, asymptomatic chronic hepatitis[6]. However, in patients with symptomatic and histologically severe chronic active hepatitis, an increased risk is present especially in presence of impaired hepatic synthetic or excretory function, portal hypertension, and bridging or multilobular necrosis on liver biopsy[7,8].

Cirrhosis

In patients with chronic liver disease, outcomes correlate with underlying hepatocellular functions. Patients with well-compensated cirrhosis may have good health for years but once a complication such as variceal hemorrhage, ascites, hepatic encephalopathy, or jaundice develops, prognosis rapidly worsens .The mortality rate associated with various non-transplant surgeries ranges from 8.3% to 25% in comparison to 1.1% in non-cirrhotic patients[4].

ESTIMATING OPERATIVE RISK IN PATIENTS WITH LIVER DISEASE

American Society of Anaesthesiologists physical status classification

It is a six category physical status classification system to assess the physical state of the patient prior to selecting for anaesthesia or performing surgery. Patients with severe liver disease are assigned a score of 3 or more. Even though, it generally correlates with perioperative mortality, this relationship is not perfect because of multiple factors influencing the perioperative outcome. This grading system is however not intended for use as a measure to predict operative risk.

In Cirrhotic patients, Teh *et al*[9] documented that an American Society of Anaesthesiologists (ASA) class of Ⅳ added the equivalent of 5.5 Model for End Stage Liver Disease (MELD) points to the mortality rate, whereas an ASA class of Ⅴ was associated with a 100% mortality rate. The influence of the ASA class was greatest in the first 7 d after surgery, after which the MELD score became the principal determinant of outcome[9]. In this study, no patient under age 30 died, and an age greater than 70 added the equivalent of 3 MELD points to the mortality rate[9].

The Child-Turcotte-Pugh scoring system

The risk of postoperative mortality and morbidity correlate(s) well with the categorization of the patient as per the Child-Turcotte-Pugh (CTP) class of cirrhosis[2,5]. A total score of 5-6, 7-9 and > 9 co-relates with CTP classification A, B, and C respectively (Table 1).

In a retrospective analysis (from 1992 to 1999) of 40 patients with cirrhosis who underwent non-hepatic surgical procedures, the presence of tense ascites, low albumin value, deranged prothrombin time, activated partial thromboplastin time, together with the emergency of the operation, was significantly correlated with a mortality of 7.1% in Child's class A, of 23% in class B, and of 84% in class C[10].

MELD scoring system

MELD score is utilized to prioritize organ allocation to the probable liver transplant recipients. The MELD score is considered objective and reliable because it is based on objective criteria, *i.e.*, serum bilirubin, serum creatinine and international normalized ratio (INR). The score can be calculated by an online MELD calculator like the one at www.unos.org/resources[11].

Table 1 Child-turcotte-pugh scoring system

Variables	Points		
	1	2	3
Encephalopathy grade	None	1 and 2	3 and 4
Ascites	Absent	Controlled	Refractory
Bilirubin (mg/dL)	1.5	1.5-2.0	> 2.0
Albumin (gm/dL)	3.5	2.0-3.5	< 2.0
Prothrombin time	1-4	4-6	> 6

Table 2 Preoperative variables and mortality rates of survivors and non-survivors of abdominal surgery

Preoperative variables	Percent of mortality if factors present	Percent of mortality if factors absent
Child class		
A	10	
B	31	
C	76	
Ascites	58	11
Emergency surgery	57	10
Bilirubin > 3 mg/dL	62	17
Albumin < 3 mg/dL	58	12
Prothrombin time > 1.5 s above control	63	18
White blood cell count > 10 000	54	19
$P < 0.01$ for all variables		

MELD = 3.78×$\log_e$ (bilirubin in mg/dL) + 11.2 × $\log_e$ (INR) + 9.57 × $\log_e$ (creatinine in mg/dL) + 6.43 (a bilirubin or creatinine value of less than 1.0 mg/dL is rounded to 1.0 mg/dL and the maximum creatinine value allowed is 4.0 mg/dL).

Recent studies suggest that MELD could be used to stratify risk in patients undergoing non transplant surgery. In a retrospective study of 140 patients with cirrhosis who underwent surgery, a 1% increase in mortality for each one-point increase in the MELD score from 5 to 20 and a 2% increase in mortality for each one-point increase in the MELD score above 20 was observed. MELD score < 10, 10-14, > 14 may correspond to CTP class A, B, C respectively[12,13].

Patients with Child Turcotte Pugh class C cirrhosis and MELD scores > 14 are generally not considered for surgical intervention. Patients with Child Turcotte Pugh class B cirrhosis and MELD scores > 8-14 have an increased perioperative risk and the indication for surgery should be assessed carefully. In patients with Child Turcotte Pugh class A cirrhosis and MELD scores of ⩽ 8, perioperative mortality is low[14].

APACHE scoring system

The Acute Physiology, Age and Chronic Health Evaluation System (APACHE Ⅲ) score can predict survival in cirrhotic patients admitted to an intensive care unit. Cirrhotic patients admitted to the medical intensive care unit are associated with high mortality rates. While both Child-Pugh and the APACHE Ⅱ scores can satisfactorily predict the outcomes for critically ill cirrhotic patients, APACHE Ⅱ is more powerful in discriminating the survivors from the non-survivors[15]. However, it has not been studied specifically in cirrhotic patients undergoing surgery.

Table 3 Preoperative variable associated with mortality

Preoperative variable	Mortality in percent if present
Pulmonary failure	100
Cardiac failure	92
Requirement of > 2 antibiotics	82
Renal failure	73
Hepatic failure	66
Gastrointestinal bleeding	86
Required second operation	81
Positive cultures	61
Blood requirement > 2 units	69
Blood requirement < 2 units	22

RISK FACTORS FOR COMPLICATION AND DEATH

Garrison *et al*[16] did a retrospective analysis on 100 patients with cirrhosis who underwent abdominal operations. Porta-systemic shunts surgery were excluded. Procedures were primarily cholecystectomies, duodenal ulcer surgery, and other miscellaneous intra-abdominal surgeries. The results of the study are shown in the Tables 2 and 3.

Ziser *et al*[4] reviewed the records of 733 patients with cirrhosis who underwent surgical procedures over an 11 years period (1980-1991) excluding liver transplantation. The mortality rate within 30 d of surgery was 11.6%. Long-term follow-up showed that most deaths occurred within the first few months after surgery, when many patients succumbed to pneumonia or renal insufficiency. Factors predictive of perioperative complications and of postoperative mortality are shown Table 4[4].

CUMULATIVE POWER OF RISK FACTORS

The probability of developing complications increased as the number of risk factors increased. About 9.3% risk of complications with 1 risk factor, 14.5% risk with 2 factors, 33.5% risk with 3 factors, 63.0% risk with 4 or 5 factors, 73.3% risk with 6 factors, 100% risk with 7 or 8 factors[4].

Aranha *et al*[17] studied a series of patients undergoing cholecystectomy. As a single quantitative measure of the severity of cirrhosis, they employed the prothrombin time. They used the criterion for the same major surgical procedure with the same surgical and anaesthetic team. Results are presented in Table 5.

Teh *et al*[9] analyzed 772 patients with cirrhosis who underwent major digestive (586), orthopedic (107) or cardiovascular surgery (79). The control group included patients with cirrhosis without any surgical procedures and those with cirrhosis and undergoing minor surgeries. The authors concluded that MELD score, ASA class and

Table 4 Factors predictive of perioperative complications and of postoperative mortality

Predictor of complications	Predictor of mortality
Child-pugh class B and C	Male gender
Ascites	Child-Pugh class B and C
Etiology of cirrhosis other than primary biliary cirrhosis	Etiology of cirrhosis other than primary biliary cirrhosis
Elevated creatinine	Ascites
Preoperative infection	Preoperative infection
Chronic obstructive pulmonary disease	Respiratory surgery
Preoperative upper gastrointestinal bleed	American Society of Anaesthesiologists physical status Ⅳ and Ⅴ
Invasiveness of surgical procedure	
Intraoperative hypotension (20% decrease of base line blood pressure for 10 min or more)	
American Society of Anaesthesiologists physical status Ⅳ and Ⅴ	

Table 5 Mortality rates in patients undergone cholecystectomy with or without cirrhosis

Variables	Mortality
Patients with normal liver function	1%
Patients with cirrhosis (PT < 2.5 s than control)	9%
Patient with cirrhosis (PT > 2.5 s than control)	83%

PT: Prothrombin time.

age were predictors of mortality. Thirty-day mortality ranged from 5.7% (MELD score < 8) to more than 50% (MELD score > 20). The relationship between MELD score and mortality persisted throughout the 20-year postoperative period[9].

NATURE OF SURGERY

The nature of surgery is an important determinant of postoperative complications. Emergency surgery is associated with a higher morbidity and mortality than elective surgery. Mansour *et al*[18] reported that emergency surgery is associated with high mortality than elective surgery: a 22% *vs* 10% for patient in child class A; 38% *vs* 30% for those in child class B; and 100% *vs* 82% for those in child class C.

Neeff *et al*[19] analyzed perioperative mortality in non-hepatic general surgical procedures in 138 patients with liver cirrhosis. About 49% (68) of the patients underwent emergency operations. There was 27.5% (38 deaths in 138 cases) of overall perioperative mortality (within 30 d of surgery) out of which 8.7% were in elective surgery (6/70) and 47% (32/68) were in emergent surgery. The similar results have also been shown by Kim *et al*[20] in a study of 53 patients with chronic liver disease who underwent emergency surgery with general anesthesia. They reported 35.8% mortality (19 out of the 53). Five deaths (9.4%) occurred within one month of surgery.

TYPE OF SURGERY

The morbidity and mortality risks are highest in patients undergoing cardiac and open abdominal surgeries including cholecystectomy, gastric resection, colectomy and hepatic resection[12]. The contributing factors proposed were laparotomy causing a greater reduction in liver blood flow and therefore more severe hepatic ischemia, and increased risk of intra-operative bleeding in the presence of portal hypertension especially in patients with previous abdominal surgery and adhesions.

ABDOMINAL WALL SURGERY

Patients with both cirrhosis and ascites have a 20% risk of developing umbilical hernia. Eker *et al*[21] conducted a prospective study to assess safety and efficacy of elective umbilical hernia repair in cirrhotic patients with ascites in 2011. The following data were collected prospectively for all patients: Child-Pugh-Turcotte classification, MELD score, kidney failure, cardiovascular comorbidity, operation-related complications, and duration of hospital stay. They concluded that elective umbilical hernia repair is safe and it is the preferred approach in cirrhotic patients with ascites.

Park *et al*[22] compared 30-d mortality among the different CTP classes, and between those with or without refractory ascites in 53 cirrhosis patients who underwent hernia repair. Seventeen patients were in CTP class A, 27 in class B, and 9 in class C. The median follow-up duration was 24 mo. Authors concluded that hernia surgery could be performed safely in CTP class A and B with low rate of recurrences, and there was no definitive increase in the operative risk in class C. Refractory ascites did not increase operative risk and recurrence rate[22].

OPEN ABDOMINAL SURGERY

The risk of surgery in patients with cirrhosis is based on studies of abdominal surgery. Neeff *et al*[19] have documented that perioperative mortality was higher after intra-abdominal than after abdominal wall operations (35% *vs* 8%, $P = 0.001$). Befeler *et al*[13] analyzed fifty-three adult patients with histologically proven cirrhosis undergoing abdominal surgery. Total 13 patients (25%) had poor outcomes including 9 deaths (17%). "Model for end-stage liver disease" score and plasma hemoglobin levels lower than 10 g/dL were found to be independent predictors of poor outcomes. A MELD score of 14 or greater was a better clinical predictor of poor outcome than CTP C. Authors concluded that patients with cirrhosis and hae-

moglobin levels lower than 10 g/dL should receive corrective blood transfusions before abdominal surgery.

Patients undergoing non transplant surgery with MELD scores lower than 10 had survival rate of 99% at 7 d, 96% at 30 d, and 92% at 90 d but survival rates were significantly lower with MELD scores of 10 or more[23].

COLORECTAL SURGERY

Nguyen *et al*[24] studied patients undergoing colorectal surgery. The mortality in patients with cirrhosis and cirrhosis with portal hypertension was significantly higher than in patients with no cirrhosis (14% and 29 % *vs* 5%, respectively). del Olmo *et al*[25] studied 135 patients with liver cirrhosis undergoing different types of non-hepatic surgeries and compared the outcomes to those without cirrhosis. Patients with cirrhosis demonstrated the increased need for intraoperative transfusion, mean length of hospital stay, postoperative complications (50.4% *vs* 29.1%) and the mortality rate (16.3% *vs* 3.5%). In a multivariate analysis it is demonstrated that high CTP score, duration of surgery and postoperative complications were independently associated with mortality in patients with cirrhosis[25].

CHOLECYSTECTOMY: OPEN OR LAPAROSCOPIC

Patients with cirrhosis who have incidental gallstones on ultrasonography should not undergo cholecystectomy unless the gallstones are symptomatic due to the possible deterioration of liver function post-operatively. Besides there is common concern whether an open or closed procedure should be done in these patients.

Poggio *et al*[26] retrospectively analyzed 50 patients who had undergone cholecystectomy for symptomatic gallstone disease. The procedure was open in half of the patients and laparoscopic in the other half. The study concluded that laparoscopic cholecystectomy is associated with statistically significant reductions in operating room time, blood loss, and length of hospital stay and is safe in patients with cirrhosis and offers advantages over an open surgical approach. Thus, laparoscopic cholecystectomy should be recommended for patients with liver disease without decompensation.

LAPAROSCOPIC CHOLECYSTECTOMY

Laparoscopic cholecystectomy carries a low mortality rate. Yeh *et al*[3], in one of the largest retrospective analyses, reported that, out of 226 patients with cirrhosis (Child-Pugh class A or B) who underwent laparoscopic cholecystectomy, only two died (0.88%). The reported mortality is low, but this figure is still significantly higher than in non-cirrhotic controls (0.01%). Suman *et al*[23] found that a preoperative MELD score of 8 or more had 91% sensitivity and 77% specificity in predicting 90-d morbidity and suggested this as the cutoff mark for considering patients with cirrhosis for laparoscopic cholecystectomy.

CARDIAC SURGERY

In 2 retrospective series of patients who underwent surgery requiring cardiopulmonary bypass, low mortality rates of 0% (0/10) and 3% (1/31) were observed in those with Child class A cirrhosis but rates were markedly increased in those with Child class B (42%-50%) and C (100%, $n = 52$) cirrhosis. In addition, more than 75% of Child class B and C patients experienced hepatic decompensation[27,28]. Increased mortality was also predicted by an increased MELD score. The best cutoff values for predicting mortality and hepatic decompensation were found to be a score greater than 7 in the CTP system and a score greater than 13 in the MELD system.

In 2007, Filsoufi *et al*[29] studied 27 patients with cirrhosis who underwent cardiac surgery. Patients were in CTP class A ($n = 10$), B ($n = 11$), and C ($n = 6$) and mean MELD score was 14.2 ± 4.2. Operative mortality was 26%. The mortality according to the CTP class was 11%, 18% and 67% for class A, B, and C respectively. No mortality occurred in patients who had revascularization without cardiopulmonary bypass. Major postoperative complications occurred in 22%, 56% and 100% for CTP class A, B, and C, respectively. Authors suggested that cardiac surgery can be performed safely in patients with CTP class A and selected patients with class B. Operative mortality remains high in class C patients.

In addition to an elevated CTP or MELD score, clinically significant portal hypertension is a contraindication to cardiothoracic surgery. Portal decompression with TIPS placement may make the risk acceptable if the CTP and MELD scores remain low[30], however, elevated right-sided cardiac pressures from cardiac dysfunction and pulmonary hypertension are absolute contraindications to TIPS placement.

In general, the least invasive option of angioplasty with or without stent placement should be considered whenever feasible in a patient with advanced cirrhosis who requires coronary artery revascularization.

Morisaki *et al*[31] conducted a retrospective study in 42 cirrhotic patients undergoing cardiovascular surgeries, of which 30 were CTP class A and 12 were CTP class B. Hospital morbidity occurred in 13 patients (31.0), including 4 who died in-hospital. The MELD score was evaluated in 25 patients. Significant differences in hospital morbidity were identified for platelet count (8.7 ± 3.8 *vs* 12.1 ± 4.2 × 10(4)/microL), MELD score (17.8 ± 5.3 *vs* 9.8 ± 4.9), operation time (370 ± 88 *vs* 313 ± 94 min), and cardiopulmonary bypass time (174 ± 46 *vs* 149 ± 53 min) in univariate analyses ($P < 0.005$). Platelet count, operation time, and age were significantly associated with hospital morbidity in multivariate analyses ($P < 0.005$). They concluded that careful consideration of operative indications and methods are necessary in cirrhotic patients with low platelet counts or high MELD scores. A high incidence of in-hospital morbidity is pre-

dicted in patients with platelet counts of less than 9.6 × 10(4)/microL or MELD scores exceeding 13.

UROSURGICAL PROCEDURES

Thirty patients with liver cirrhosis who underwent transurethral resection of the prostate (TURP) were compared to 150 patients without liver cirrhosis. There was 6.7% mortality at 30 d in cirrhotic group compared to 2% mortality in patients without cirrhosis. This study indicates that TURP in patients with liver cirrhosis is associated with increased mortality[32].

PULMONARY PROCEDURES

Liu *et al*[33] retrospectively analyzed 59 adults with cirrhosis undergoing chest tube placement. Variables that were investigated included reason for chest tube placement, complications developing while having the tube in place, and outcome. Their results demonstrated that out of 59 subjects 3 were classified as having CTP class A cirrhosis, 31 as CTP class B cirrhosis, 25 as CTP class C cirrhosis. Indications for having a chest tube placed were hepatic hydrothorax (n = 24), pneumothorax (n = 9), empyema (n = 8), video-assisted thoracoscopy (VAT n = 7), non-VAT (n = 5), and hemothorax (n = 3). Serum total bilirubin levels, presence of porto-systemic encephalopathy, and CTP C classification were predictors of mortality. Mortality was seen in 5 out of 31 CTP class B subjects (16%), and in 10 out of 25 CTP class C subjects (40%).

In a retrospective analysis of 37 patients with comorbid cirrhosis who underwent curative surgery for primary lung cancer, occurrence of postoperative complications like liver failure, bleeding and critical infection were studied to determine the factors predicting liver cirrhosis-related complications in the early postoperative period[34]. Liver cirrhosis related complications occurred in seven of the 37 patients (18.9%). Transient liver failure occurred in two patients (5.4%) after pulmonary resection. Acute intrathoracic bleeding occurred in four cases (10.8%). Two patients died (5.4%) due to sepsis. Preoperative total bilirubin ($P < 0.05$), and indocyanine green retention rate at 15 min ($P < 0.05$) were significantly higher in patients with liver failure. Only serum value of total bilirubin was an independent risk factor ($P < 0.05$) by multivariate analysis. In predicting death from infection, only preoperative nutritional status was a significant risk factor ($P < 0.05$). It was suggested that to avoid postoperative cirrhosis related complications, preoperative preparation to improve their liver function and nutrition status is essential.

TRAUMA

Trauma patients found to have cirrhosis at laparotomy are at increased risk for morbidity and mortality. In one study, the overall mortality rate was 45%, significantly higher than of a matched control population (24%)[35]. Mortality and morbidity rates were increased even for patients considered to have relatively minor trauma. The authors recommended that trauma patients found to have cirrhosis at laparotomy be admitted to the intensive care unit for close monitoring and aggressive management irrespective of the severity of their injuries.

ANESTHESIA

The risk of surgery cannot be separated from the risk of anesthesia. Sedatives, narcotics, and intravenous induction agents are generally well tolerated in patients with compensated liver disease but must be used with caution in patients with decompensated hepatic dysfunction, because they may cause prolonged depression of consciousness and precipitate hepatic encephalopathy.

Blood levels of narcotics that undergo high first-pass extraction by the liver, increase as hepatic blood flow decreases. Elimination of benzodiazepines that undergo glucuronidation (*e.g.*, oxazepam, lorazepam) is unaffected by liver disease, whereas the elimination of those that do not undergo glucuronidation (*e.g.*, diazepam, chlordiazepoxide) is prolonged in liver disease. Long acting narcotics and sedatives should (therefore) be avoided in cirrhotic patients. However, the use of various narcotics like Fentanyl, Sufentanil and sedatives like Oxazepam, Lorazepam, in conjunction with anesthetics is recommended, because their actions are less prolonged in patients with liver disease[36].

Anesthesia can affect the liver functions by reducing its blood flow. In healthy volunteers, hepatic blood flow decreases by 35%-42% in the first 30 min of induction of anesthesia[37]. Studies in animals have shown that under the conditions of stress, hepatic blood flow increases to compensate for the reduced portal blood flow but patients with liver disease, especially cirrhosis under the influence of anesthesia cannot compensate for the reduced portal blood flow, which may cause hepatic dysfunction[38]. The anesthetic agents Halothane and Enflurane reduce hepatic arterial blood flow. These effects are minimal with Isoflurane.

Acute hepatitis associated with the administration of halothane is believed to be caused by immune sensitization to trifluoroacetylated liver proteins formed by oxidative metabolism of halothane by cytochrome P450 2E1 in genetically predisposed persons[39]. With this notable exception, few data suggest that either the choice of anesthetic agent or mode of administration (inhaled or spinal) influences surgical outcome in patients with liver disease[40].

Inhalational agents Isoflurane, Desflurane and Sevoflurane undergo hepatic metabolism, extent of which is 0.2% for isoflurane, 2%-4% for Enflurane, and 20% for Halothane[41] presumably, this leads to a lesser incidence of drug-induced hepatitis. Therefore, Isoflurane has become the inhalation agent of choice in patients with liver disease.

Propofol is an excellent anesthetic agent of choice in patients with liver disease, because it retains a short half-life even in patients with decompensated cirrhosis[42].

The volume of distribution of non-depolarizing muscle relaxants is increased in patients with liver disease, and therefore larger doses may be required initially to achieve adequate neuromuscular blockade. The actions of neuromuscular blocking agents may be prolonged in patients with liver disease because of reduced pseudocholinesterase activity, decreased biliary excretion, and larger volume of distribution. Atracurium and cisatracurium are the preferred muscle relaxants in patients with liver disease because neither the liver nor the kidney is required for their elimination. Doxacurium is the preferred muscle relaxant in longer procedures such as liver transplantation, as it is metabolized by the kidney.

No correlation could however be established in patients with cirrhosis undergoing cardiac surgery and hepatic decompensation or mortality between the use of Enflurane, Isoflurane, Fentanyl, Sufentanil, Midazolam or Morphine[28]. The type of anesthetic management either general anesthesia, regional anesthesia, or monitored anesthesia care did not affect the mortality in one of the largest reported series of 733 patients[4].

CONCLUSION

The literature on patients with liver disease undergoing surgical procedures emphasizes that CTP status and MELD score correlates well with the perioperative morbidity and mortality and are reasonably good predictors of the operative risk. Various open abdominal and even cardiac surgeries can be performed in patients of Child A status and MELD score < 8 with low perioperative mortality. In patients with Child C status and MELD score > 14, elective surgeries other than liver transplant should be avoided. Acute liver failure is a contraindication for any surgical intervention other than liver transplant. Surgery in acute hepatitis should be deferred till it resolves. Laparoscopic and abdominal wall surgeries can be safely performed as compared to open abdominal surgeries in patients of cirrhosis with Child A and B status. Emergency procedure carries significantly higher risk of perioperative mortality and morbidities in patients with cirrhosis irrespective of their Child status or MELD score. The type of anesthetic management either general anesthesia, regional anesthesia, or monitored anesthesia care do not have correlation with mortality.

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On biomarkers and pathways in rectal cancer: What's the target?

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Abstract

In spite of tremendous progresses in surgical and chemo-radiotherapeutic regimens, rectal cancer still suffers from high relapse and mortality rates, and metastatic disease is incurable. Here we assess some of the most recent and validated biomarkers and potential targets studied in rectal cancer, and provide comments to a recent monographic topic covering several aspects of colorectal cancer, published in *Current Cancer Drug Targets*.

Key words: Rectal cancer; Colorectal surgery; Chemotherapy; Targeted molecular therapy; Biological markers

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COMMENTARY ON HOT ARTICLES

The management of rectal adenocarcinoma has undergone tremendous improvements in the last decade, especially through the advancement of surgical techniques combined with a better defined timing of medical treatment. Still, rectal adenocarcinoma affects about 140 000 new patients each year in Europe, and has a 5-year overall survival of 54%[1]. Currently, standard treatment for stage Ⅱ and Ⅲ rectal cancer includes pre-operative (neo-adjuvant) treatment with 5-fluorouracyl or capecitabine, in combination with ionizing radiation (IR) therapy[1]. The introduction of biological drugs targeting receptor kinases like epidermal growth factor receptor (EGFR) (cetuximab, panitumumab[2,3]), or their ligands, like vascular endothelial growth factor (VEGF) (bevacizumab[4]), has shown promising results. Nonetheless, DNA damaging agents like capecitabine and IR have maintained their roles as the single, most effective modalities of treatment in locally advanced rectal cancer, together with surgery.

In spite of the above mentioned advancements, a large fraction of the patients who undergo regimens containing these agents does not respond to their action, strongly suggesting that rectal tumors can harbor resistance mechanisms *ab initio*, or are able to acquire them in the course of therapy. Microarray studies have been used in the effort of creating classifiers and predictors to treatment response, but the results are scarcely consistent and have not been validated extensively[5,6]. Small datasets, different technical and statistical approaches, and inhomogeneous treatment modalities might have contributed to suboptimal results in data interpretation. Among the best

studied molecular markers of rectal cancer (p53[7], p21[8], Bax and Mib[9], p27[10], thymidylate synthase[11], EGFR[12] or VEGFR[13]) few have shown to hold some promise in rectal cancer prognostic assessment before standard regimens, and their advantage over conventional pathological staging procedures to predict outcome has not yet been validated in large, prospective studies.

Identifying new biomarkers in rectal cancer management could be advantageous for several reasons: (1) the a priori knowledge of tumor resistance to neoadjuvant treatment would spare patients useless and potentially toxic pharmacologic agents, and could lead to the choice of different strategies (*e.g.*, immediate or more radical surgical intervention or shorter courses of adjuvant chemotherapy in complete responders to neoadjuvant treatment); (2) understanding the molecular alterations which constitute the ground of rectal cancer may allow the use of new biologically targeted agents, in combination with surgical resection; and (3) last but not least, the cost/effectiveness ratio of proposed management strategies could be better assessed, in a time when the economic burden of the health care system is steadily growing toward unmanageable dimensions.

The increasingly appreciated complexity of colorectal cancer systems biology is well addressed by the recently published monographic topic, published in *Current Cancer Drug Targets* (*CCDT*)[14-19]. Here, the contributing Authors deal with two of the mainstays of the new "smart weaponries" in colorectal cancer treatment: the EGFR pathway[15] and VEGF signaling[14]. Moreover, two new "hot topics" are covered: the concept of synthetic lethality[18] and the translational potential of mathematical simulations of signaling networks involved in the neoplastic process[19]. Synthetic lethality refers to the ideal situation where the inactivation of one protein product or another does not affect cancer viability, whereas the combined deficiency of both proteins is deadly for the cancer cell[20,21]. The first successful application of this model has been observed in the treatment of breast cancer 1 gene (*BRCA1*)-deficient breast cancer with poly (ADP-ribose) polymerase (PARP) inhibitors[22,23]. The difficulty of finding new synthetic lethal interactions lies in the combinatorial complexity of identifying pairs of protein products showing such properties. While high throughput silencing RNA based screenings may be of help in this field[24], a deepened understanding of how molecular networks interact with each other and dynamically react to internal and external stimuli[25] (such as chemotherapy, IR or targeted agents) is of the essence to generate plausible hypotheses before testing them in "real life". This last issue is well addressed by Parodi[16] in the aforementioned topic.

Finally, an "old dog with potentially new tricks" is also presented in the above referenced *CCDT* issue: targeting DNA damage repair pathways and cell cycle checkpoints in colorectal cancer[17]. While the Reader could reasonably object that such targets are nothing else than those aimed at for the last fifty years by conventional chemotherapy, an essential and relatively overlooked concept is highlighted: since cancer is ontologically characterized, among other features, by genomic instability and mutations[26], intrinsic deficits must exist in tumors which hamper their ability to repair their own genetic information. As a consequence, cancer cells should be more prone than healthy tissues to be killed by DNA damaging agents. It is therefore likely that, with a better knowledge of "what's wrong", physicians could be able to predict "what would be right" in individual cases. Again, PARP inhibition in breast cancer with *BRCA1* germline alterations has been the proof of principle, but it would be simplistic to assume that no other DNA damage repair genes are altered in somatic tumors, hence showing similar properties. This, in turn, leads directly back to one of the main questions in the management of rectal cancer, *i.e.*, why do some cases exhibit exquisite sensitivity to neoadjuvant chemo-radiation, whereas others appear to be completely resistant?

In conclusion, the recent topic appeared in *CCDT* is an interesting and comprehensive reading, that covers several essential aspects of what is currently known about colorectal cancer, and provides the Reader with an updated overview of its biology and of the future roads that may potentially lead to the complete cure of most patients affected by rectal cancer. The greatest endeavor of research in rectal cancer remains that of combining big, well-conducted prospective clinical trials with large breadth ancillary biologic studies. Only this synergism between basic and clinical analytic efforts will lead to the discovery and validation of new biomarkers with a real impact in everyday oncological and surgical practice.

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Non-steroidal anti-inflammatory drugs in colorectal surgery: A risk factor for anastomotic complications?

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Abstract

In a recent article, Gorissen *et al* report on 795 patients with primary colorectal anastomosis operated on during the period 2008-2010 for different colorectal conditions at two centres. The leakage rate was significantly higher among patients who were administered non-steroidal anti-inflammatory drugs (NSAIDs) in the perioperative course. A dose-response relationship could also be traced, where longer NSAID use yielded a higher risk of anastomotic breakdown. However, as this study is observational in design, confounding by indication may be present and there is also a risk of residual confounding from unmeasured covariates. Moreover, the question whether different affinity for the cyclooxygenase enzyme is important in different NSAIDs seems to be largely unanswered. The results, conclusions and clinical relevance of the aforementioned study, including the possible effects of different types of NSAIDs, are discussed. While acknowledging that this study represents the best attempt so far in establishing the causal relationship between perioperative NSAID use and anastomotic leakage, the need for further research in this important area is underlined.

Key words: Cancer; Colon; Non-steroidal anti-inflammatory drugs; Leakage; Rectum; Anastomotic leak

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COMMENTARY ON HOT ARTICLES

We read with interest the recent article by Gorissen *et al*[1] from the Netherlands reporting data from two teaching hospitals concerning use of non-steroidal anti-inflammatory drugs (NSAIDs) and anastomotic leakage in colorectal surgery.

Anastomotic leakage is a feared complication that increases morbidity, mortality and healthcare costs[2,3]. Identified risk factors include malnutrition, smoking, comorbidity and, in rectal cancer surgery, male gender, lack of a protective stoma, and anastomotic level[4-7]. Whether or not the level of vessel ligation is a risk factor is still under debate[8].

NSAIDs are currently widely used in perioperative analgesia as a means of providing effective pain control while decreasing the need for opioid drugs and, subsequently, reducing the risk of nausea, constipation and ileus[9,10]. Since NSAIDs interfere with the normal inflammation present in wound healing, it is not illogical to infer a risk of impaired anastomotic healing. This

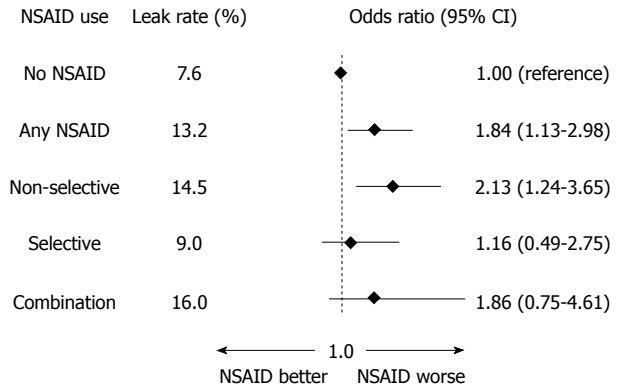

Figure 1 Multivariable logistic regression with non-steroidal anti-inflammatory drugs as exposure and anastomotic leakage as outcome in 795 patients operated on with a primary colorectal anastomosis[1]. NSAIDs: Non-steroidal anti-inflammatory drugs.

possible negative factor must be thoroughly scrutinized, especially since any detrimental effects on anastomotic integrity may overshadow the positive effects of opioid-sparing NSAIDs.

NSAIDs are a heterogeneous group of drugs, traditionally subdivided by their effects on the enzymes of the cyclooxygenase (COX) class. The COX enzymes are responsible for the production of prostaglandin H2, the first step in the prostanoid biosynthesis. With the revelation that most of the adverse effects of NSAID used seemed to be linked to decreased COX-1 activity, and that the beneficial anti-inflammatory effects seemed to be associated with inhibition of COX-2, the development of selective COX-2 inhibitors was initiated. Several of the classical NSAIDs have been reappraised and turned out to be mostly COX-1 selective, which thus reflected their tendency to cause gastrointestinal side effects. However, the positive effects of selective COX-2 inhibition have subsequently been questioned, as any lesser rate of gastrointestinal adverse effects may have been outweighed by negative effects such as increased risk of cardiovascular events[11].

As regards to colorectal surgery, recent retrospective clinical studies have also indicated a negative effect on anastomotic healing[12-14], as well as some, but not all, experimental investigations[15-17]. In these studies, COX-2 inhibitors in particular have been implicated, as these have been compared unfavourably with mostly COX-1 selective compounds; more specifically, the use of celecoxib and diclofenac compared to ibuprofen seemed to be associated with high leakage rates[12-14]. This is of special note, as the classical NSAID diclofenac usually is classified as "weakly COX-2 selective" along with celecoxib, while ibuprofen is classified as "weakly COX-1 selective"[18]. Thus, some of the debate regarding potential effects on anastomotic healing has revolved around not only NSAID use in general, but also the different affinity for the two main COX enzymes.

In the present article, Gorissen *et al*[1] analyzed retrospectively 795 patients who underwent primary colorectal anastomosis during a three-year period from 2008 to 2010 at two Dutch teaching hospitals. Indications for surgery included both benign disease and colorectal malignancy, and elective as well as emergency surgery was performed. All patients were treated according to a fast-track surgery protocol including epidural anaesthesia, while the use of NSAIDs was not standardized, and was thus administered as per physician preference. The patients were divided into four groups according to NSAID use, where the terms "non-selective" and "selective" NSAIDs were used to differentiate older and newer classes of NSAIDs, roughly differentiated by the later being ostensibly more selective towards COX-2. The largest group was non-users (n = 471). Of the NSAID users, 201 patients used non-selective NSAIDs, 79 used selective COX-2 inhibitors and 44 used both non-selective and selective drugs. It should be noted that the authors defined diclofenac as a non-selective NSAID while meloxicam and celecoxib were categorized as selective NSAIDs.

The overall leakage rate was 9.9% (10.0% for right colonic, 8.7 for left colonic and 12.4 for rectal anastomoses). Among the patients who were not administered NSAIDs, the leakage rate was 7.6%, while users of any NSAID sustained a leakage rate of 13.2%; the multivariable odds ratio (OR) with 95%CIs was 1.84, 1.13 to 2.98. The leakage rates for non-selective NSAID, selective NSAID and combination users amounted to 14.5, 9.0, and 16%, respectively, with corresponding ORs (and 95%CIs) of 2.13 (1.24 to 3.65), 1.16 (0.49 to 2.75) and 1.86 (0.75 to 4.61), respectively (Figure 1). Interestingly, an analysis of the duration of NSAID use yielded significant differences between use of any NSAID for three days or more compared with use for only one or two days, with longer use being associated with a higher rate of anastomotic leakage (16.6% *vs* 10.0%).

In the current study, the use of NSAIDs as compared to non-use seemed to be associated with an increased risk of leakage from colorectal anastomoses. This in our opinion is, to date, the best designed and most adequately powered study to establish this relationship. However, the question of whether COX-1 and/or COX-2 inhibitors are responsible for this increase in risk is still debatable. The stratification into "non-selective", "selective" and "combination" users dilutes the statistical power, which may in itself make any conclusions hard to justify; moreover, the decision to classify diclofenac as a non-selective NSAID may have confounded these results, as diclofenac is comparable to both celecoxib and meloxicam regarding COX-2 affinity[11]. Taking this into consideration, the current study may not quite disprove that truly selective NSAIDs are a risk factor for leakage. The aforementioned retrospective studies, in which the use of diclofenac and celecoxib has been compared to ibuprofen, are therefore difficult to relate to the current study, as ibuprofen did not seem to be used.

Furthermore, the patient population in this study is quite heterogeneous, as patients undergoing both elective and emergency surgery and with malign and benign disease were included. Nevertheless, the authors have

adjusted for known confounders including *e.g.*, resection type, but residual confounding is hard to rule out due to the observational nature of the study. This study design is also subject to confounding by indication, duly acknowledged by the authors, as NSAIDs might have been administered because of increasing pain due to leakage or factors leading to leakage, *e.g.*, anastomotic tension. Surgical technique might also be of concern, as there is a surprisingly high rate of leaks from the colonic anastomoses, amounting to about 10%. This may explain the postoperative mortality of 4.2% for all patients, which does not compare well to even population-based figures[19].

In conclusion, the authors have produced the best attempt so far in establishing the causal relationship between postoperative NSAID exposure and colorectal anastomotic leakage. However, this result must be interpreted with caution and might not yet justify the discontinuance of established practices of administering NSAID in this setting. Although this study corroborates the general perception that NSAID use may increase the risk of anastomotic leakage, there is still considerable uncertainty regarding the effects of inhibiting the COX subtypes. Further research is certainly warranted and could include large register studies as well as prospective studies with meticulous collection of data concerning NSAID exposure, including timing of administration postoperatively, type of substance, duration and dosage. Ideally, a multi-centre randomized controlled trial would be suitable in order to ultimately answer the question of whether any NSAID use causes anastomotic leakage; however, one might question the ethics of performing such a study, considering the mounting observational evidence against NSAID use.

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Incorporating dynamics for predicting poor outcome in acute liver failure patients

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Abstract

Acute liver failure (ALF), also known as fulminant hepatic failure (FHF), is a devastating clinical syndrome with a high mortality of 60%-90%. An early and exact assessment of the severity of ALF together with prediction of its further development is critical in order to determine the further management of the patient. A number of prognostic models have been used for outcome prediction in ALF patients but they are mostly based on the variables measured at one time point, mostly at admission. ALF patients rarely show a static state: rapid progress to a life threatening situation occurs in many patients. Since ALF is a dynamic process, admission values of prognostic variables change over time during the clinical course of the patient. Kumar *et al* developed a prognostic model [ALF early dynamic (ALFED)] based on early changes in values of variables which predicted outcome. ALFED is a model which seems to be worthwhile to test in ALF patients in other parts of the world with different aetiologies. Since the exact pathophysiology of ALF is not fully known and is certainly complex, we believe that adding promising variables involved in the pathophysiology of ALF to the dynamic approach might even further improve prognostic performance. We agree with Kumar *et al* that an improved dynamic prognostic model should be based on simplicity (easily to be performed at the bedside) and accuracy. Our comments presented in this paper may be considered as recommendations for future optimization of ALF prediction models.

Key words: Acute liver failure; Fulminant hepatic failure; Prediction models; Prognosis; Prediction

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COMMENTARY ON HOT ARTICLES

We read with great interest the recent article by Kumar *et al*[1] about the derivation and validation of an early dynamic model for predicting outcome in patients with acute liver failure (ALF).

ALF, also known as fulminant hepatic failure (FHF), is a devastating clinical syndrome with a high mortality of 60%-90%, depending on the aetiology and the clinical experience of the reference center[2,3]. Most frequent causes of death are brain oedema, systemic inflammatory response and multiple organ failure. In the Western world (United States and Europe) annually about 7500 patients suffer from ALF. "Spontaneous recovery" occurs in a minority of these patients. In most cases liver transplantation (LT) remains the only life saving treat-

ment of irreversible ALF. However, due to lack of sufficient donors only 20% of patients can be directly treated with LT. As a result, many patients die while on the donor waiting list.

An early and exact assessment of the severity of ALF together with prediction of its further development is critical in order to determine the further management of the patient such as (bio) artificial liver support and/or urgent LT. The timely prediction of spontaneous recovery helps to prevent LT and also the need for lifelong immunosuppressive therapy. Predicting whether the patient with ALF will require LT or will survive by only intensive medical care remains, however, challenging.

A number of prognostic models have been used for outcome prediction in ALF patients to select patients in need for LT. The most widely applied ones are the King's College Criteria (KCC), Clichy criteria, and the Model for End-Stage Liver Disease (MELD). The models have shown inconsistent reproducibility of prognostic accuracy, and the need for a better prognostic model remains[4,5]. Prognostic models used in literature are mostly based on the variables measured at one time point, mostly at admission. ALF patients rarely show a static state: rapid progress to a life threatening situation occurs in many patients. Since ALF is a dynamic process, admission values of prognostic variables change over time during the clinical course of the patient.

Kumar *et al*[1] developed a prognostic model [ALF early dynamic (ALFED)] based on early changes (during first 3 d of hospitalisation) in values of variables which predicted outcome independently at admission in a prospective cohort of 244 patients with ALF (mainly caused by acute viral hepatitis) and validated it in a prospective observational study of 136 ALF patients with comparable aetiology. The model was constructed based on whether the levels of predictive variables remained persistently high or increased over 3 d of hospitalisation above the discriminatory cut-off values identified in this study. Liver transplantation was not available at their centre, and the only possible outcome was recovery or death. The authors found that early changes of prognostic markers predict outcome better than the static baseline levels. Their model consists of clearly defined and routinely available predictors. This is a worthwhile study in agreement with the concept that the use of dynamic changes over time of predictors should improve prognostic performance. This observation is supported by the systematic review of Minne *et al*[6] that underlined the association between the dynamics of the Sequential Organ Failure Assessment score with hospital mortality in the intensive care.

The ALFED model of Kumar *et al*[1] consists of four variables, which is in line with the known pathophysiology of ALF, namely hyperammonemia as a consequence of impaired hepatic urea synthesis and contributing to the development of hepatic encephalopathy (HE); hyperbilirubinemia as a consequence of impaired biliary excretion and coagulopathy as a consequence of decreased protein synthesis, especially of clotting factors, expressed by international normalized ratio (INR).

We assessed the quality of the ALFED model and its development process based on a framework for the assessment of the quality of and reporting on prognostic models[7]. Kumar *et al*[1] clearly describe the setting and the study population; they report the type of the study (prospective) and the number of patients and events (deaths/survivals). Based on the results of our previous work[8] we are aware that many studies often do not report the definition of the disease. Kumar *et al*[1] give a clear definition of ALF as well as of the variables, including their units. Furthermore it could be inferred which variables were continuous or categorical. Initial variables included routinely available factors, which were already known to be important. However, we could not find any information about whether there were missing values, and if so, where, and what was done to them. This information should not be neglected when presenting the development of a model.

Kumar *at al*[1] clearly report the type of the model, its intended use as well as its derivation and evaluation process and present the model's formula which can be used to make prediction. ALFED is a logistic regression model used for predicting the outcome of ALF patients based on the prospectively collected development set. First univariate analyses were performed to determine the variables which were statistically significantly (at the 0.05 level) associated with the outcome. Next, a multivariable logistic regression model was developed with the significant predictors using a stepwise forward selection procedure. We recommend using an information criterion (such as the Akaike Information Criterion) in the (*e.g.*, backward, stepwise) selection process instead of relying on *P*-values $\leqslant 0.05$ in univariate analysis.

It is important to perform validation of the model, *e.g.*, asses a model's discrimination and calibration performance in order to reinforce model credibility before its use in clinical practice. Discrimination is the ability of the model to assign higher predicted probabilities of the outcome (*e.g.*, death) in patients actually having the outcome than in those not having it. The discrimination of the ALFED model was assessed by the area under the receiver operator characteristic (AUROC) curve. Calibration measures the proximity between the predicted probabilities and the actual risk of a group of similar patients. Calibration was assessed using an observed versus predicted plot and the Hosmer-Lemeshow statistic. Kumar *et al*[1] report also on other statistical performance measures based on a given cut-off point, such as: sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio and diagnostic accuracy. Kumar *et al*[1] performed temporal validation of the model[9], which means on a different sample collected later, but from the same population of the developmental dataset. However, the two samples significantly differed in INR, arterial pH and ammonia, mean MELD value, hepatitis E virus aetiology and mortality.

The ALFED model was also compared with the established prognostic models KCC and MELD. The results

of this comparison showed that performance of MELD and KCC criteria (based on AUROC and the above mentioned statistical performance measures determining its prognostic accuracy) was inferior to the ALFED model in the two cohorts, although no statistical testing was attempted for comparison.

Since the exact pathophysiology of ALF is not fully known and is certainly more complex than the above mentioned disturbances in ammonia (HE), bilirubin metabolism and coagulation, our hypothesis is that extending the dynamic approach to other variables involved in the pathophysiology of ALF might still improve prognostic performance. For example, biomarkers of the inflammatory response of ALF may further improve the predictive performance of such a model, for example plasma ratio of interleukin (IL)-6/IL-10[10-12]. In addition, the impaired capacity of the ALF patient to maintain metabolic homeostasis might be included by using hyperlactatemia for example. We agree with Kumar *et al*[1] that an improved dynamic prognostic model should be based on simplicity (easily to be performed at the bedside) and accuracy.

Although ALFED should be still tested on patients with other aetiologies (*e.g.*, paracetamol overdose), it seems to be a valuable step forward.

Based on our above considerations we conclude that ALFED is a well constructed and well reported model which seems to be worthwhile to test in ALF patients in other parts of the world with different aetiologies. In addition, we believe that adding promising variables involved in the pathophysiology of ALF to the dynamic approach might even further improve prognostic performance. Our comments may be considered as recommendations for future research on developing ALF prediction models.

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BRIEF ARTICLE

Does perioperative prostaglandin E1 affect survival of patients with esophageal cancer?

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Abstract

AIM: To detect the effect of intraoperative prostaglandin E1 (PGE1) infusion on survival of esophagectomized patients due to cancer.

METHODS: In this preliminary study, a double blinded placebo based clinical trial was performed. Thirty patients with esophageal cancer scheduled for esophagectomy *via* the transthoracic approach were randomized by a block randomization method, in two equal groups: PGE1 group - infusion of PGE1 (20 ng/kg per minute) in the operating room and placebo group - saline 0.9% with the same volume and rate. The infusion began before induction of anesthesia and finished just before transfer to the intensive care unit. The patients, anesthetist, intensive care physicians, nurses and surgeons were blinded to both study groups. All the patients were anesthetized with the same method. For postoperative pain control, a thoracic epidural catheter was placed for all patients before induction of anesthesia. We followed up the patients until October 2010. Basic characteristics, duration of anesthesia, total surgery and thoracotomy time, preoperative hemoglobin, length of tumor, grade of histological differentiation, disease stage, number of lymph nodes in the resected mass, number of readmissions to hospital, total duration of readmission and survival rates were compared between the two groups. Some of the data originates from the historical data reported in our previous study. We report them for better realization of the follow up results.

RESULTS: The patients' characteristics and perioperative variables were compared between the two groups. There were no significant differences in age (P = 0.48), gender (P = 0.27), body mass index (P = 0.77), American Society of Anesthesiologists physical status more than Ⅰ (P = 0.71), and smoking (P = 0.65). The PGE1 and placebo group were comparable in the following variables: duration of anesthesia (277 ± 50 *vs* 270 ± 67, P = 0.86), duration of thoracotomy (89 ± 35 *vs* 96 ± 19, P = 0.46), duration of operation (234 ± 37 *vs* 240 ± 66, P = 0.75), volume of blood loss during operation (520 ± 130 *vs* 630 ± 330, P = 0.34), and preoperative hemoglobin (14.4 ± 2 *vs* 14.7 ± 1.9, P = 0.62), respectively. No hemodynamic complications requiring an infusion of dopamine or cessation of the PGE1 infusion were encountered. Cancer variables were compared between the PGE1 and placebo group. Length of tumor (11.9 ± 3 *vs* 12.3 ± 3, P = 0.83), poor/undifferentiated grade of histological differentiation [3 (20%) *vs* 3 (20%), P = 0.78], disease stage Ⅲ [5 (33.3%), 4 (26.7%), P = 0.72] and more than 3 lymph nodes in the resected mass [3 (20%) *vs* 2 (13.3%), P = 0.79] were similar in both groups. All the patients were discharged from hospital except one patient in the control group who died because of a post operative myocardial infarction. No life threatening postoperative complication occurred in any patient.

The results of outcome and survival were the same in PGE1 and placebo group: number of readmissions (2.1 ± 1 *vs* 1.9 ± 1, *P* = 0.61), total duration of readmission (27 ± 12 *vs* 29 ± 12, *P* = 0.67), survival rate (10.1 ± 3.8 *vs* 9.6 ± 3.4, *P* = 0.71), overall survival rate after one year [8 (53.3%) *vs* 7 (47%), *P* = 0.72], overall survival rate after two years [3 (20%) *vs* 3 (20%), *P* = 0.99], and overall survival rate after three years [0 *vs* 1 (6.7%), *P* = 0.99], respectively.

CONCLUSION: In conclusion, PGE1 did not shorten or lengthen the survival of patients with esophageal cancer. Larger studies are suggested.

Key words: Prostaglandin E1; Esophagectomy; Cancer; Survival; Surgery

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INTRODUCTION

Esophageal cancer is the eighth most common cancer worldwide. In spite of improvements in systemic chemotherapy and radiotherapy, multimodality treatment and surgical processes, its mortality is considerable[1].

Prostaglandin E1 (PGE1) is derived enzymatically from fatty acids with effects on immunity and the vascular system[2-4]. In several previous reports, administration of a low dose of PGE1 has been shown to be advantageous in early postoperative periods, such as improved oxygenation[5,6].

Attenuation of systemic inflammatory response syndrome[7], prevention and treatment of postoperative acute respiratory distress syndrome[8], prevention of ischemic injuries[2], shorter stays in the intensive care unit and hospital[9,10] and reduced mortality rate[10,11] have been reported.

PGE1 is administered in surgeries due to malignancies[5,10]. Its complex and comprehensive effects on the immune system have been shown previously but its long term effects on these patients have not been reported previously. We could not find any reports that directly assessed the effects of PGE1 on cancer cells *in vitro* or *in vivo*. There is no report about PGE1 effects on survival of cancer patients. Therefore, we decided to measure the survival of patients who were esophagectomized because of cancer and received PGE1 during the operation in a preliminary study. We followed up the patients who enrolled in our previous trial[10] and measured their survival and outcome.

MATERIALS AND METHODS

We used the same patients and study from our previous publication[10] and the current manuscript is only the report of the follow up of the previous study. The study was approved by the ethical committee of Tehran University of Medical Sciences and written informed consent was obtained from each patient. This preliminary randomized placebo based trial was performed from October 2007 to October 2010 in a university referral cancer center. All patients scheduled for a transthoracic approach esophagectomy due to cancer were entered in the study. Exclusion criteria from the study were age older than 75 years, preoperative chemotherapy or radiotherapy, steroid administration before operation, any antibiotic therapy (except preoperative prophylactic antibiotic administration), esophageal reconstruction using a segment of jejunum or colon, applying laparoscopy or thoracoscopy, trans-hiatal esophagectomy, any acute or chronic inflammatory or infectious disease and any acute or chronic lung disease.

By application of a block randomization method, thirty patients were allocated to two equal groups: the PGE1 and placebo group. All the patients were followed after randomization and nobody was excluded from the study (Figure 1). In the PGE1 group, PGE1 (Prostin VR; Pharmacia and Upjohn, Puurs, Belgium) was infused with a dose of 20 ng/kg per minute in the operating room. The infusion began before induction of anesthesia and finished just before transfer to the intensive care unit. In the placebo group, saline 0.9% with the same volume and rate was infused. The patients, anesthetist, intensive care physicians, nurses and surgeons were blinded to the intervention group.

A thoracic epidural catheter was placed for all the patients before induction of anesthesia, with a midline approach through vertebral interspaces between T6-L1. Then, an epidural bolus dose of 3-4 mL of bupivacaine 0.5% was injected and the catheter was fixed to the skin.

Patients were premedicated with midazolam 0.05 mg/kg and sufentanil 0.2 μg/kg five minutes before induction of anesthesia. Anesthesia was induced by thiopental sodium 5 mg/kg. Cisatracurium 0.15 mg/kg was given to facilitate tracheal intubation. General anesthesia was maintained by 1.5%-2.0% (inspired concentration) isoflurane in oxygen. Additional cisatracurium and sufentanil were given when required.

In the postoperative period, patients were admitted to an intensive care unit and received similar care according to a specified protocol. After discharge from hospital, patients were followed up in a postoperative surgery clinic and by phone until October 2010.

Basic characteristics, duration of anesthesia, total surgery and thoracotomy time, preoperative hemoglobin, length of tumor, grade of histological differentiation,

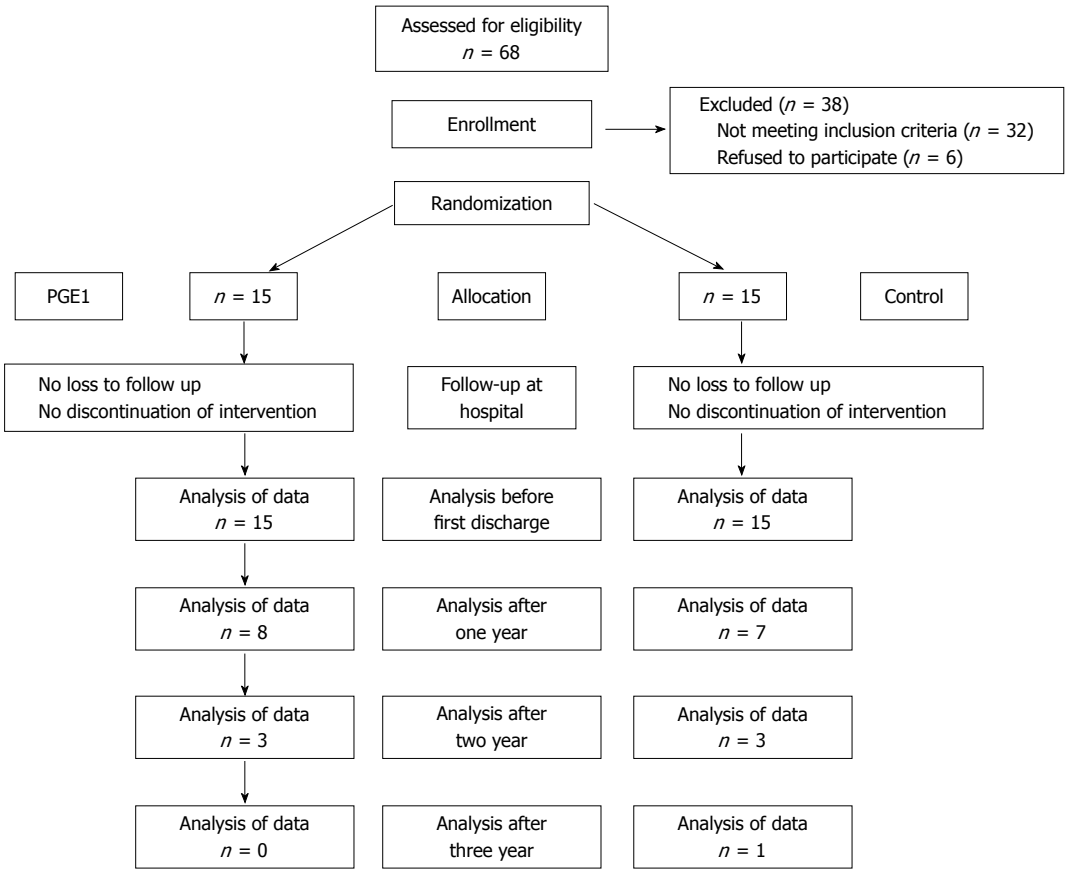

Figure 1 Trial profile of the 68 patients

disease stage, number of lymph nodes in resected mass, number of readmissions to hospital, total duration of readmission and survival rates were compared between the two groups.

The main goal of this study was assessment of PGE1's effects on survival of the patients. However, in this preliminary study we did not calculate the sample size.

Statistical analysis

The continuous variables are presented as mean ± SD. Kolmogorov-Smirnov test for goodness of fit to normal distribution was performed and normality was obtained for all measurements. Student's *t*-test was used for comparison of the means of continuous variables. Categorical variables are given as counts and group comparisons were made with the χ^2 test. All calculations were performed with SPSS version 16 (SPSS Inc., Chicago, IL, United States). A probability level P value < 0.05 was considered to indicate statistical significance. Also, some of the data originates from the historical data reported in our previous study[10], such as Table 1, and we report them for better realization of the follow up results.

RESULTS

The patients' characteristics and perioperative variables are depicted (Table 1). There were no significant differences in basic characteristics. Duration of anesthesia, thoracotomy and operation, volume of blood loss during operation and preoperative hemoglobin were comparable between the two groups. No hemodynamic complications requiring an infusion of dopamine or cessation of the PGE1 infusion were encountered.

Cancer variables are shown (Table 2). Length of tumor, grade of histological differentiation, disease stage and number of lymph nodes in the resected mass were similar in both groups.

All the patients were discharged from hospital except for one patient in the control group who died because of a post operative myocardial infarction. No life threatening postoperative complication occurred in any patient.

Patients were followed up for nearly 3 years and the results of outcome and survivals are presented (Table 3). PGE1 and placebo groups were comparable in the number of readmissions to hospital, total duration of readmission and different survival rates ($P > 0.05$).

DISCUSSION

In this preliminary study, we did not find that an intraoperative infusion of PGE1 had any significant effects on outcomes or survival parameters of esophagectomized patients in comparison with a placebo.

Surgery related stress may cause a metabolic and systemic inflammatory response in major operations[12]. It is believed that prostaglandins, cytokines, chemokines,

Table 1 Baseline characteristics and perioperative variables

	PGE1 group (n = 15)	Control group (n = 15)	P value
Age (yr)[1]	54 ± 9	57 ± 8	0.48
Gender (male)[2]	6 (40)	9 (60)	0.27
Body mass index (kg/m^2)[1]	31 ± 4	32 ± 3	0.77
ASA physical status (> I)[2]	9 (60)	10 (66.7)	0.71
Smoking[2]	2 (13.3)	4 (26.7)	0.65
Preoperative hemoglobin (g/dL)[1]	14.4 ± 2	14.7 ± 1.9	0.62
Duration of anesthesia (min)[1]	277 ± 50	270 ± 67	0.86
Duration of operation (min)[1]	234 ± 37	240 ± 66	0.75
Duration of thoracotomy (min)[1]	89 ± 35	96 ± 19	0.46
Blood loss (mL)[1]	520 ± 130	630 ± 330	0.34

[1]mean ± SD, Student's *t*-test; [2]Frequency (percent), χ^2 test or Fisher's exact test. PGE1: Prostaglandin E1; ASA: American Society of Anesthesiologists.

Table 3 Outcome and survival variables

	PGE1 group (n = 15)	Control group (n = 15)	P value
Number of readmissions to hospital[1]	2.1 ± 1	1.9 ± 1	0.61
Total duration of readmission (d)[1]	27 ± 12	29 ± 12	0.67
The survival rate (mo)[1]	10.1 ± 3.8	9.6 ± 3.4	0.71
The overall survival rate after 1 yr	8 (53.3)	7 (47)	0.72
The overall survival rate after 2 yr	3 (20)	3 (20)	0.99
The overall survival rate after 3 yr	0	1 (6.7)	0.99

[1]mean ± SD, Student's *t*-test; [2]Frequency (percent), χ^2 test or Fisher's exact test. PGE1: Prostaglandin E1.

cyclooxygenase and other products of an uncontrolled inflammatory response could advance cancer progression *via* immunosuppression, resistance to apoptosis and promotion of angiogenesis[13]. However, the role of acute inflammation, especially due to the perioperative period and surgical stress, in recurrence or metastasis of cancer has not been fully studied.

In the perioperative period, an increase in the level of cytokines, such as interleukin (IL)-6 and IL-8, in combination with several other changes in the inflammatory system could account for profound suppression of natural killer cytotoxic activity[14]. PGE1 regulates the immune response to tissue trauma by various mechanisms. It modifies the release of inflammatory mediators[15], shortens the duration of systemic inflammatory response syndrome, and also attenuates the severity of systemic inflammatory response syndrome after esophagectomy[7]. It has been shown that infusion of PGE1 attenuates the increase in serum levels of IL-6[5,10] and IL-8[16]. Therefore, in a perioperative acute inflammatory condition, PGE1 may attenuate the effect of the inflammatory system on suppression of natural killer (NK) cytotoxic activity. So, it could be supposed that infusion of PGE1 indirectly could prevent the defects in NK cytotoxic activity and consequently improve defence against cancerous cells.

The results of this preliminary study should be interpreted cautiously because of several limitations in the study. This study was based on a small sample size. We did not calculate the proper sample size, with considering

Table 2 Cancer variables

	PGE1 group (n = 15)	Control group (n = 15)	P value
Length of tumor (cm)[1]	11.9 ± 3	12.3 ± 3	0.83
Grade of histological differentiation[2]			
Good	3 (20)	4 (26.7)	0.78
Intermediate	9 (60)	8 (53.3)	
Poor	2 (13.3)	3 (20)	
Undifferentiated	1 (6.7)	0 (0)	
Disease stage[2]			
ⅡA	8 (53.3)	10 (66.7)	0.72
ⅡB	2 (13.3)	1 (6.7)	
Ⅲ	5 (33.3)	4 (26.7)	
Number of lymph nodes in resected mass[2]			
0	5 (33.3)	4 (26.7)	0.79
1-3	7 (46.7)	9 (60)	
⩾ 4	3 (20)	2 (13.3)	
Pathological T1[2]	2 (13.3)	2 (13.3)	0.75
Pathological T2	1 (6.7)	3 (20)	
Pathological T3	12 (80)	10 (66.7)	
Pathological N1[2]	5 (33.3)	6 (40)	0.99

[1]mean ± SD, Student's *t*-test; [2]Frequency (percent), χ^2 test or Fisher's exact test. PGE1: Prostaglandin E1.

survival parameters and outcome as the main goal. We have not considered other important factors, such as the disease state, as well as postoperative treatment and care.

In conclusion, PGE1 did not shorten or lengthen the survival of patients with esophageal cancer. The study of the effects of PGE1 on the promotion of cancer is recommended.

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COMMENTS

Background

Esophageal cancer is the eighth most common cancer worldwide. In spite of improvements in systemic chemotherapy and radiotherapy, multimodality treatment and surgical processes, its mortality is considerable. Prostaglandin E1 (PGE1) is derived enzymatically from fatty acids with effects on immunity and the vascular system. PGE1 is administered in surgeries due to malignancies. Its complex and comprehensive effects on the immune system have been shown previously but its long term effect on these patients has not been reported previously.

Innovations and breakthroughs

In a perioperative acute inflammatory condition, PGE1 may attenuate the effect of the inflammatory system on suppression of natural killer (NK) cytotoxic activity. So, it could be supposed that an infusion of PGE1 indirectly could prevent the defects in NK cytotoxic activity and consequently improve defence against cancerous cells.

Applications

PGE1 did not shorten or lengthen the survival of patients with esophageal cancer. The study of the effects of PGE1 on the promotion of cancer is recommended.

Peer review

The aim of this study was to assess the effects of PGE1 on survival of esophageal cancer patients who underwent surgery. It was previously reported that perioperative administration of PGE1 reduced the risk of postoperative com-

plications, yet the long term effect of PGE1 on patient survival has not been studied.

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BRIEF ARTICLE

Managing acute colorectal obstruction by "bridge stenting" to laparoscopic surgery: Our experience

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Abstract

AIM: To verify the clinical results of the endoscopic stenting procedure for colorectal obstructions followed by laparoscopic colorectal resection with "one stage anastomosis".

METHODS: From March 2003 to March 2009 in our surgical department, 48 patients underwent endoscopic stenting for colorectal occlusive lesion: 30 males (62.5%) and 18 females (37.5%) with an age range from 40 years to 92 years (median age 69.5). All patients enrolled in our study were diagnosed with an intestinal obstruction originating from the colorectal tract without bowel perforation signs. Obstruction was primitive colorectal cancer in 45 cases (93.7%) and benign anastomotic stricture in 3 cases (6.3%).

RESULTS: Surgical resection was totally laparoscopic in 69% of cases (24 patients) while 17% (6 patients) of cases were video-assisted due to the local extension of cancer with infiltrations of surrounding structures (urinary bladder in 2 cases, ileus and iliac vessels in the others). In 14% of cases (5 patients), resection was performed by open surgery due to the high American Society of Anesthesiologists score and the elderly age of patients (median age of 89 years). We performed a terminal stomy in only 7 patients out of 35, 6 colostomies and one ileostomy (in a total colectomy). In the other 28 cases (80%), we performed bowel anastomosis at the same time as resection, employing a temporary ileostomy only in 5 cases.

CONCLUSION: Colorectal stenting transforms an emergency operation in to an elective operation performable in a totally laparoscopic manner, limiting the confection of colostomy with its correlated complications.

Key words: Colorectal cancer; Laparoscopy; Colonic stenting; Intestinal obstruction; Endoscopy

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INTRODUCTION

Colorectal obstruction represents a common problem due to pelvic neoplasms, such as gynecological, prostatic, colorectal and urinary bladder in 90% of cases[1-3] or due to bowel inflammatory conditions, such as Crohn's disease and ischemic or diverticular stenosis. Colorectal cancer causes a complete or incomplete obstruction in 8%-29% of cases[4-8] and obstruction represents 85% of surgical emergencies for colon cancer[9]. Bowel obstruction leads to some complications like dehydration, hypo-

volemic shock, renal or pulmonary acute failure, intestinal perforation, peritonitis *etc*. These conditions are a worse prognostic factor for elderly patients with high American Society of Anesthesiologists (ASA) or Acute Physiology and Chronic Health Evaluation score or with locally advanced or metastatic cancer (almost 40% of this kind of patients) above all[6,10-13]. For these reasons, emergency management of this kind of condition is characterized by a high morbidity (40%-60%) and mortality rate (3%-19%)[14] but, for some authors, also 27%-40%[1,9,15-19], considering that the mortality rate for the same operation performed electively ranges from 0.9%-6%[1,13,20]. In addition, it is peremptory to stress that these conditions are correlated to a high temporary or definitive colostomy rate (24%-40%), with negative impact on the quality of life for the patient (in terms of limited social and sexual life), on the social costs and with the consequent necessity for the patient to undergo one or more operations to re-establish intestinal continuity[1,6,21,22]. Consequently, these reasons have promoted research for alternative therapeutic ways; contemporaneously, the encouraging results of a stenting procedure achieved in esophageal, duodenal, biliary and vascular districts have led to experimental use of endoscopic stenting initially as palliative treatment of tumoral colonic stenosis and subsequently as preparation for curative colonic surgery ("bridge to surgery")[23,24].

In fact, the possibility of not performing a surgical decompression of the bowel using an endoscopic stent allows for a palliation therapy in patients with severe comorbidity or advanced cancer, avoiding a surgical emergency and allowing elective surgery with several benefits. This procedure allows improvement in the general condition of patients who are often wasted and dehydrated, reducing post operative mortality and morbidity; it allows diagnostic procedures with complete staging and the optimal pre-operative cleansing of the large bowel, allowing anastomosis in one stage and avoiding a temporary ileo or colostomy (one stage procedure). Although an intestinal stent is expensive, its use decreases the overall cost because it reduces the costs of surgery, hospital stay and intensive therapy from 19.7% to 28.8%, as reported by some authors[25-27], and the costs of ileo or colostomy with its correlated complications (prolapse, stenosis, cutaneous irritation). In some studies, the cost of palliative stenting is less than surgical palliation by 50% and the cost of the "bridge to surgery treatment " is less than surgery, from 12%-20%[26,28-30].

Since Dohmoto *et al*[31] first described the successful stenting of a rectal occlusive tumor in inoperable patients in 1991, several studies have been performed to evaluate the safety and the efficacy of the new promising procedure[32-34].

During these years, techniques and devices were modified; from rigid and plastic endoprosthesis commonly used in the tracheobronchial, esophageal and vascular district[27,35] (with a perforation rate of 22%[36] and increased risk of dislocation, obstruction and inhibition of peristalsis) to modern self expanding flexible metal stents easier to use in flexure and tight stenosis and with a considerably lower rate of complications[37].

The only disadvantage of this kind of stent is the neoplastic growth through the mesh; for this reason, polyurethane covered stents have been successively proposed.

At the beginning, the flexure or descending colon localization was a contraindication to the stenting procedure but actually any anatomic site is precluded. In fact, although at least 70% of obstructive lesions occur in the left colon, similar lesions of other colonic segments, including the ascendant colon, are successfully treated[26,38]. Right sided occlusions might be managed by an emergency operation with a limited morbidity and mortality rate compared to left sided resections. Other than site lesion, the length also does not constitute a contraindication to stenting, even if lesions less than 3 cm are technically more manageable[26]. The success rate reported in the literature ranges from 64% to 100%[10,34,35,39].

The stenting procedure is considered the first line treatment for neoplastic stenosis, both as a bridge to surgery and as palliative therapy in patients not amenable for surgery for oncological reasons, poor general conditions or in the case of no informed consent[21,25,32,38,40].

This approach has been recently criticized in the palliative use of a stent because, except for occlusion, it does not solve symptoms like pain, rectal tenesmus, bleeding and anemia; despite that, it has been approved by the FDA[21].

The only contraindication is the presence of colic perforation which requires an immediate laparotomy or laparoscopy.

The use of a stent in benign pathology has sporadic confirmation in the literature[41-44] but is controversial due to the lack of randomization studies and there being other ways of avoiding occlusion. For example, dilatation is considered a valid alternative in Crohn's stenosis, with a success rate of 80%-90%[45,46] but with short-term results.

MATERIALS AND METHODS

The aim of our study was to verify the clinical results of the endoscopic stenting procedure for colorectal obstructions followed by laparoscopic colorectal resection with "one stage anastomosis".

From March 2003 to March 2009 in our surgical department, 48 patients underwent endoscopic stenting for colorectal occlusive lesions: 30 males (62.5%) and 18 females (37.5%) with an age range of 40-92 years (median age 69.5). All patients enrolled in our study were diagnosed with an intestinal obstruction originating from the colorectal tract without bowel perforation signs. Diagnosis of intestinal obstruction was made on the basis of clinical history, symptoms and physical examination of the patient, who underwent radiological examinations like abdominal X-ray, colon X-ray evaluation with

Table 1 Site of obstruction

Patients	Site of obstruction
2	Transver secolon
3	Splenic flexure
29	Descending/sigmoidcolon
9	Upper rectum
5	Middle rectum

Table 2 Type of resections

	Laparoscopic	Open	Assisted
Right colectomy	3	-	-
Segmentary resection	3	2	-
Left colectomy	9[1]	-	1[1]
Proctectomy	7[1]	-	2[1]
Hartmann	2[2]	1[2]	3[2]
Total colectomy	-	2[3]	-

[1]End to end colorectal anastomosis Knight Griffen; [2]Vascular deficit in 1 case, peritoneal carcinomatosis in 2 cases, local advanced rectal cancer in 3 cases; [3]Left sided obstruction with cecal diastatic rupture.

a water-soluble gastrografin enema and, in some cases, an abdominal computed tomography scan. The obstruction was primitive colorectal cancer in 45 cases (93.7%) and benign anastomotic stricture in 3 cases (6.3%). All patients underwent a cleansing enema before the endoscopic procedure and had a pre-medication intravenous injection of 2 mg of Midazolam® (Midazolam-hameln pharmaceuticals gmbh, Hameln, Germany) during the examination without anesthetic assistance. The procedure was done using an endoscope because it allowed easier prosthetic placement, mainly for tumor obstruction located above the rectal peritoneal reflection, allowing visualization in real time of the successfully stenting and allowing the biopsy of the lesion. Stents positioned endoscopically are limited in their gauge because they have to pass inside the endoscope.

The procedure was always performed using a guidewire inserted through the endoscope duct, moving it beyond the obstruction and then inserting the stent using Seldinger's technique. We have never performed any kind of dilatation or laser treatment of the obstruction to allow stenting. We have always utilized the same Wallflex® system (Boston Scientific Corporation) of 25 mm gauge, with variable length according to the site and the extension of the obstruction, provided with a releasing device through the scope through-the-scope. This kind of stenting system costs about 1630 Euro.

Twenty-four hours after stenting, we performed an abdominal X-ray to evaluate the correct placement of prosthesis and the absence of free intra abdominal air. Then the patient can resume oral intake, a half liquid diet, and can complete the diagnostic course and eventually have pre-surgical preparation.

The technical success rate (correct placement and expansion of prosthesis) of our series was about 95.8%

Table 3 Histological characteristics of specimen *n* (%)

Grading and TNM (UICC system)	
G2	22 (62.9)
G2/3	8 (22.8)
G3	5 (14.3)
T2	2 (5.7)
T3	21 (60)
T4	12 (34.3)
N^+	18 (51.4)
N1	9 (25.7)
N2	9 (25.7)
M^+	8 (22.8)

TNM: Tumor node metastasis; UICC: Union for International Cancer Control.

and clinical success rate was about 100% (relief of occlusion and abdominal deflating). The only two failures occurred in a patient affected by obstructed stenosis that was not amenable to be crossed by a ground wire; therefore, he underwent an emergency operation. Complications occurred in 2 patients (4.2%): one dislocation and one perforation. The latter case was caused by a cecal break due to air insufflation during stenting. In 13 cases (27%), the stenting procedure represented the only therapeutic and palliative option because the patients were in a poor clinical condition, were old and affected by serious comorbidity. The remnant of 35 patients (73%) consequently underwent surgical bowel resection and the median time of bridge to surgery was 9.2 d, ranging from 2 to 78 d. Of these patients, twenty were male (57.1%) and fifteen female (42.9%), with a median age of 69 years. Sixteen were ASA Ⅱ, thirteen ASA Ⅲ and six ASA Ⅳ. The site of obstruction is shown in Table 1.

Surgical resection was totally laparoscopic in 69% of cases (24 patients) while 17% (6 patients) of cases were video-assisted due to the local extension of cancer with infiltrations of surrounding structures (urinary bladder in 2 cases, ileus and iliac vessels in the others). In 14% of cases (5 patients), resection was performed by open surgery due to the high ASA score and the elderly age of patients (median age of 89 years). We performed a terminal stomy in only 7 of 35 patients, 6 colostomies and one ileostomy (in a total colectomy). In the other 28 cases (80%), we performed bowel anastomosis at the same time of resection, employing a temporary ileostomy only in 5 cases; the latter presented a higher than 3 risk factor for anastomotic leakage.

The type of surgical resection is shown in Table 2. Mean operative time was 220 min for laparoscopic surgery and 183 min for open surgery. The histological characteristics of cancer are represented in Table 3.

At the time of diagnosis, 22.8% of patients had distant metastasis. 51.4% of cases were found to have a metastatic lymph node (25.7% N1 and 25.7% N2) with a median of 18.2 lymph nodes isolated for specimen (range 7-35). The number of lymph nodes removed during laparoscopic resection was mild major of that removed in open surgery, 19.1 *vs* 17.9.

Table 4 Complications

Complications	*n*
Major complications	
Acute myocardial infarction	1
Anastomotic leak[1]	1
Anastomotic dehiscence	1
Minor complications (fever, anemia requiring blood transfusion, prolonged post surgical ileus, wound infection)	5
Total (%)	8 (22.8%)

[1]Subclinical anastomotic leak in patient with ileostomy.

The margin free from disease was on average 4.4 cm (range: 2-8.5 cm) without any significant difference between the open and laparoscopic approach (4.1 cm open *vs* 4.8 cm laparoscopic).

Median hospital stay after laparoscopic resection was 8.3 d and 12.1 d after open surgery. Median time of flatus was 3 d, resumption of oral intake was within 4 d, bladder catheter was usually removed on the fourth day and drainage tube on the sixth day (range: 4-8) and in these cases, the laparoscopic approach highlighted a short mean time. Complications occurred in 8 patients (22.8%), as shown in Table 4, and there was no mortality in our series.

DISCUSSION

In the last decade, the high mortality and morbidity rate occurring after emergency colorectal resection for intestinal obstructions have become well-known as complications related to colostomy, including alterations of the sexual and quality of life[19]. These events can be limited by performing the "one stage resection" technique with an intra-operating wash out[47], but it extends the surgical time and does not reduce complications due to bacterial migration, paralytic ileus, colonic handling etc. Other palliative procedures, such as endoscopic dilatation, laser, electrocauterization, cryo and photodynamic therapy[27,48], require repeated applications without immediately resolving the stenosis like the stenting procedure does.

Seventeen years after the intuition of Dohmoto, following the earlier studies by Spinelli *et al*[49] in 1992, Itabashi *et al*[50] in 1993 and Saida *et al*[51] in 1996, and after the multicenter trials conducted by Mainar *et al*[52] in 1999, colorectal stenting has been demonstrated to be a safe and useful procedure, with a success rate ranging from 64% to 100%[11,27]. This procedure allows resolution of a bowel obstruction, a unique palliative treatment in cases of inoperable patients, and as preparation for surgery to reduce complications and colostomies related to an emergency operation. Endoscopic stenting manages a critical bowel occlusion by performing a suitable intestinal cleansing, a colonic decompression and, in the same breath, balances the general clinical condition of the patient with correct hydration, nutrition and antibiotic therapy in order to perform a colonic resection in safe conditions. The stenting procedure increases the primary anastomosis rate and reduces the colostomy rate[47,53,54]. Recent meta-analysis trials[6,17,55] have demonstrated that endoscopic stenting significantly reduces the mean length of hospital stay by at least of 6-8 d, reduces the recourse to the intensive care unit, the morbidity and mortality rate and the colostomy rate from 24% to 8.2%.

Patients who underwent endoscopic stenting before surgery had ileus and consequently oral intake resumed earlier, a mean of 5 d earlier compared to patients who underwent emergency colonic resection without a preventative endoscopic procedure[56,57].

Some authors[58] claim that stent expansion could promote a local or distal diffusion of neoplastic cells due to a squeezing out effect or to possible bowel perforation (risk of 4%), but other recent studies[6,55,59,60] have demonstrated statistically significant differences of about 3 and 5 years survival rate between the use or not of a stenting procedure.

Complications due to stenting occur in about 30% of cases[10,34] and they are divided into early or late, depending on if they occur within or over 30 d. Early complications are more frequent in malignant neoplastic stenosis, while in benign stenosis, they are later[11,44].

Major complications are: dislocation or migration, perforation, break, re-obstruction with "cheesewiring" (cancer growth through the spaces of a metallic uncovered stent), fistulization, anorectal pain, incontinence and bleeding. Minor complications are intestinal hematoma and ulcerations.

Dislocation, reported in 4%-40% of cases[21,23,34,61], frequently occurs in benign pathology because tumoral growth maintains the stent in situ, otherwise it becomes malignant pathology, chemo treated or after employing laser therapy because the cancer reduction causes increase of the bowel lumen, promoting stent dislocation[10,21,38,44,62]. Another cause of migration may be the presence of hard feces or the diameter and type of stent employed.

Perforation, reported in 1%-17% of cases[6,10,21,38,44,51,63], is due to dilatation being performed before stent positioning and is also due to insertion, expansion and mucosal erosion caused by the stent. Perforation represents the most serious complication and it may spread tumor cells and result in a prompt emergency operation. A bowel stenosing lesion localized in the upper peritoneal reflection has a major risk of being perforated during the stenting procedure.

Late obstruction is a complication reported in the literature, with a rate ranging from 7% to 30%[38,44], is caused by the cancer growth through the stent (cheesewiring) and the use of a covered stent reduces this kind of complication but increases the migration risk[64].

Tumoral growth, both inside and around the stent, is a potential limiting factor of palliation therapy because it requires periodical substitution of the stent associated with Argon laser treatment[33,59,65]. To avoid pain, it is essential that the terminal portion of the stent is positioned at least above the dentate line. For this reason, it is difficult to stent a tumoral lesion located within 5 cm

from the anal margin, considering an overlap of 1 cm is required.

The cumulative mortality rate due to the stenting procedure ranges from 0.4 % to 1%[10-39].

Even with the best results and limited complication rate, the colonic stenting procedure is still not widely accepted because it may be problematic to institute an emergency multidisciplinary approach and achieve a suitable training level. It is most common to perform a Hartmann colic resection or colostomy alone in high risk patients because large and controlled randomized trials are being waited for before introducing this approach in clinical practice.

In the last decade, the laparoscopic approach has been also extended to oncological colorectal surgery, maintaining the specific advantages of laparoscopy as a minor surgical trauma, major comfort for patients (minor pain and minor analgesic needs), best esthetic result, minor hospital stay and minor post recovery complications but, at the same time, showing its safety, feasibility and oncological radicality available with the open approach.

Same randomized trials demonstrate the superiority of laparoscopic colectomy for cancer *vs* an open colectomy in terms of relapse and disease free survival[47,66,67].

In our experience, other than the above mentioned advantages, the stenting procedure has allowed us to do laparoscopic colorectal resection.

For the last decade in our surgical department, we have preferred the laparoscopic approach, whether to manage elective colorectal cancer or an emergency, to perform about 80% of total abdominal operations. One limit to advise against laparoscopy in managing intestinal occlusion is the distension of the small bowel resulting in a decreasing field of view. The stenting procedure allows avoidance of this problem.

In our study, we performed laparoscopic colon resection in 24 of 35 cases. Our results confirm stenting is a safe and feasible procedure, with an open conversion rate of 20% and without any intra-operating complications.

In conclusion, the treatment of stenotic colorectal obstruction by endoscopic decompression and subsequent laparoscopic resection with anastomosis represents a safe procedure, joining the advantages of respective mini invasive maneuvres with excellent clinical results.

Colorectal stenting transforms an emergency operation burdened with remarkable risks, complications and mortality to an elective operation performable in a totally laparoscopic manner, limiting the confection of colostomy with its correlated complications.

COMMENTS

Background

Colorectal cancer causes a complete or incomplete obstruction in 8%-29% of cases and the obstruction represents 85% of surgical emergencies in colon cancer. Bowel obstruction leads to some complications, like dehydration, hypovolemic shock, renal or pulmonary acute failure, intestinal perforation, peritonitis etc. that increases the morbidity and mortality rate. For this reason, the encouraging results of a stenting procedure achieved in esophageal, duodenal, biliary and vascular districts have led to experimental use of endoscopic stenting initially as palliative treatment of tumoral colonic stenosis and subsequently as preparation to curative colonic surgery, "bridge to surgery".

Research frontiers

Since Dohmoto *et al*[31] first described the successful stenting of a rectal occlusive tumor in an inoperable patient in 1991, several studies have been performed to evaluate the safety and efficacy of the new promising procedure. During these years, techniques and devices were modified; from rigid and plastic endoprothesis commonly used in the tracheobronchial, esophageal and vascular district to modern self expanding flexible metal stents easier to use, even in flexure and tight stenosis. The only disadvantage of this kind of stent is the neoplastic growth through the mesh; for this reason, polyurethane covered stents are successively proposed.

Innovations and breakthroughs

Colorectal stenting transforms an emergency operation burdened with remarkable risks, complications and mortality to an elective operation performable in a totally laparoscopic manner, limiting the confection of colostomy with its correlated complications.

Applications

Endoscopic stenting manages a critical bowel occlusion, performing a suitable intestinal cleansing, colonic decompression and, in the same breath, balancing the general clinical condition of the patient with correct hydration, nutrition and antibiotic therapy in order to perform a colonic resection in safe conditions. The stenting procedure increases the primary anastomosis rate, reduces the colostomy rate and significantly reduces the mean length of hospital stay, the recourse to an intensive care unit, the morbidity and mortality rate and the colostomy rate.

Peer review

This is a good study in which the authors analyze the effective safety and utility of the endoscopic colorectal stenting procedure, transforming an emergency operation to an elective operation performable in a laparoscopic manner.

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BRIEF ARTICLE

Ambulatory laparoscopic cholecystectomy: An audit of day case *vs* overnight surgery at a community hospital in Japan

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Abstract

AIM: To evaluate the applicability and safety of ambulatory laparoscopic cholecystectomy (LC) and to compare day case and overnight stay LC.

METHODS: Data were collected retrospectively and consecutively for day case and overnight stay LC patients from July 1, 2009 to April 30, 2011. Outcomes were analyzed for patient demographics, operation time, blood loss during operation and frequency and reasons for unexpected or prolonged hospitalization in each group.

RESULTS: There was no hospital mortality and no patient was readmitted with serious morbidity after discharge. 50 patients received a day case LC and 19 had an overnight stay LC. There was a significant difference in age between both groups ($P < 0.02$). There were no significant differences between the day case LC performed ($n = 41$) and failed ($n = 9$) groups and between the day case LC performed and the one night stay LC ($n = 12$) groups. There was a significant difference in age between the one night stay and more nights stay LC groups ($P < 0.05$). Thus, elderly patients showed a tendency to like to stay in hospital rather than being a day case. The proportion of unexpected or prolonged hospitalization was not significantly different between the day case and overnight stay LC groups, when the patient's request was excluded.

CONCLUSION: Day case LC can be performed with a low rate of complications. In overnight stay patients, there are many who could be performed safely as a day case. Moreover, we need to take special care to treat elderly patients.

Key words: Laparoscopic cholecystectomy; Day case *vs* overnight

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INTRODUCTION

Laparoscopic cholecystectomy (LC) has now become the standard procedure for the surgical treatment of symptomatic gallstone patients[1,2]. Because of the smaller scars and reduced postoperative pain, introduction of the LC procedure has resulted in a shorter hospital stay, a shorter period of convalescence and an earlier return to work. LC has been performed regularly as ambulatory surgery in patients with uncomplicated gallstone disease in the United States[3] and parts of Europe[4]. Ambulato-

ry LC is performed in one hospital by day case[5-7], while in another hospital by overnight stay[8,9]. Both have not yet to gain acceptance in Japan.

The aim of this retrospective study was to evaluate the applicability and safety of ambulatory LC at a community hospital in Japan and to compare between day case and overnight stay LC.

MATERIALS AND METHODS

Ethics

This work was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved ethically by the Nagoya Kyoritsu Hospital Trust. All patients provided informed written consent.

Patients and methods

We have performed day case or overnight stay LC since 2001. From July 1, 2009, we have innovated a new technique of transversus abdominis plane block (TAP block)[10], a local anesthetic procedure, to decrease postoperative pain. Therefore, in this retrospective study, we reviewed the patients who underwent day case or overnight stay LC from July 1, 2009 to April 30, 2011. LC was performed on 113 patients at our hospital in this period. Of 113 patients, 69 underwent a day case or overnight stay LC, according to the following exclusion criteria (Figure 1). The other patients underwent LC as an inpatient procedure.

The requisite indication for day case or overnight stay LC was chronic symptomatic calculous gallbladder disease. The absolute contraindications to exclude day case or overnight stay LC were: (1) acute cholecystitis; (2) American Society of Anesthesiologists (ASA) grade > Ⅱ; (3) previous upper abdominal surgery; (4) living alone; and (5) living further than 3 h by car from our hospital. Sixty-nine patients decided of their own free will to undergo either day case or overnight stay LC.

Preoperative diagnostic examinations included routine blood tests, liver function tests, ultrasonic scan and computed tomography of the liver and the bile ducts, and drip infusion cholangiography using computed tomography (DIC-CT) or magnetic resonance cholangiography (MRC) to detect choledocholithiasis. An endoscopic retrograde cholangiography was performed prior to the surgery to remove choledochus calculi in patients diagnosed by DIC-CT or MRC.

The LC surgeries were performed first on a morning theatre list to ensure proper postoperative recovery prior to discharge. All patients underwent LC using a standard four ports (5 mm ports) technique. CO_2 pneumoperitoneum was established with a maximum pressure of 12 mmHg and the camera was placed in the umbilical area. The trocar site to raise the bottom of the gallbladder was under the right costal arch in the midclavicular line. The left-hand port site was used to bring the portal triad into view, while the port under the xyphoid process, 2 cm under the midline, was used for dissecting Calot's triangle. An ordinary electrosurgical device was used for the dissection. The umbilical port was opened under direct incision to remove the nylon bag which contained the resected gallbladder. Intraoperative cholangiography was not performed in any case because choledochus calculi were removed prior to LC.

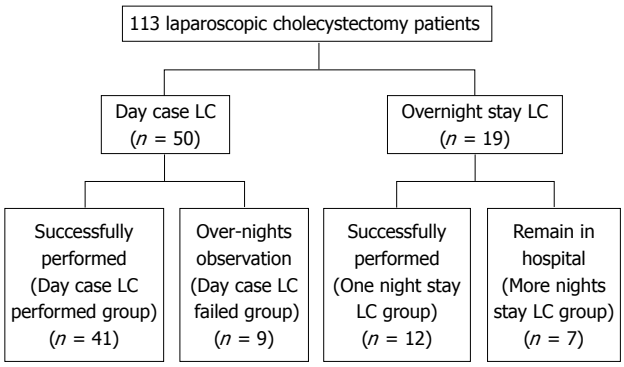

Figure 1 Flow-chart of the patients. LC: Laparoscopic cholecystectomy.

As far as anesthesia is concerned, general anesthesia was adapted to suit the cardiovascular circumstance of each patient and a subcostal TAP block was performed using 25 mL of 0.5% ropivacaine in both sides of the abdomen immediately after induction of general anesthesia. This subcostal TAP block was performed under ultrasound by identifying the transversus abdominis plane between internal oblique muscle layer and transversus abdominis muscle layer in the abdominal wall[10].

The postoperative pain control regime consisted of 4 mg of lornoxicam 3 times a day as a regular prescription for the first 3 d and then on an as required basis, together with 50 mg of diclofenac sodium suppository as a one shot medicine.

The patients were divided into two groups, the day case LC group and overnight stay LC group in the first place. Then, each group was divided into two groups by whether it was successfully performed or not. The day case LC group was divided into day case LC performed group and day case LC failed group, and the overnight stay LC group was divided into one night stay LC group and more nights stay LC group (Figure 1).

Data included patient characteristics, operation time, blood loss during LC and frequency and reasons for unexpected or prolonged hospital stay in each group.

Statistical analysis

All values were given as mean ± SD. Student's t test and χ^2 test were used to compare the two groups. $P < 0.05$ was considered statistically significant.

RESULTS

None of the patients required conversion to open cholecystectomy. There was no hospital mortality and no patient was readmitted with serious morbidity after discharge. Fifty of 69 patients were operated on as a day case LC. Their mean age was 53.6 ± 14.5 years with a

Table 1 Comparison of the characteristics of the patients in different groups

	Day case LC group (n = 50)	Overnight stay LC group (n = 19)	P value	Day case LC performed group (n = 41)	Day case LC failed group (n = 9)	P value	One night stay LC group (n = 12)	More nights stay LC group (n = 7)	P value
Age (yr)	53.6 ± 14.5	62.7 ± 13.9	< 0.02	53.5 ± 14.9	54.3 ± 13.7	NS	57.9 ± 12.8	70.9 ± 12.8	< 0.05
Gender									
Male	24	9	NS	20	4	NS	5	4	NS
Female	26	10		21	5		7	3	
Operation time (min)	108.4 ± 41.7	107.4 ± 39.3	NS	106.4 ± 40.7	117.7 ± 47.7	NS	100.3 ± 42.9	119.4 ± 31.5	NS
Blood loss during the operation (mL)	6.6 ± 22.4	12.8 ± 20.5	NS	7.6 ± 24.6	2.0 ± 2.4	NS	10.9 ± 22.5	16.1 ± 17.6	NS

LC: Laparoscopic cholecystectomy; NS: Not significant.

Table 2 Reasons for unexpected hospital stay in the day case laparoscopic cholecystectomy group and prolonged hospital stay in the overnight stay laparoscopic cholecystectomy group

	Day case LC group	Overnight stay LC group
Nausea and vomiting	4	1
Necessity of clinical observation following drain insertion	3	1
Patient's request	2	5

LC: Laparoscopic cholecystectomy.

range of 28-78 and there were 24 males and 26 females. Their mean operation time was 108.4 ± 41.7 min and mean blood loss during the operation was 6.6 ± 22.4 mL. Another 19 patients were operated on as an overnight stay LC. Their mean age was 62.7 ± 13.9 years with a range of 37-80 and there were 9 males and 10 females. Their mean operation time was 107.4 ± 39.3 min and mean blood loss during the operation was 12.8 ± 20.5 mL. There were no significant differences in gender, operation time and blood loss during the operation but age (P < 0.02) between the day case and overnight stay LC group (Figure 1 and Table 1) was statistically significant.

In 50 patients of the day case LC group, 41 patients were discharged on the same day within 8 h after assessment by the operating surgeon, based on a modified post-anesthesia discharge scoring system (MPADSS)[11]. Their mean age was 53.5 ± 14.9 years with a range of 28-78 and there were 20 males and 21 females. Their mean operation time was 106.4 ± 40.7 min and mean blood loss during the operation was 7.6 ± 24.6 mL. Another 9 patients needed to be admitted to hospital for 2.1 ± 2.0 nights. The reasons for 4 one night admissions were nausea and vomiting, those for another 3 for 4 and 5 nights admission were the requirement of clinical observation following drain insertion due to bile spill, and those for the other 2 were at the patient's request. The term "patient's request" means hospitalization regardless of approval for discharge by the operative surgeon according to MPADSS (Table 2). Their mean age was 54.3 ± 13.7 years with a range of 31-74 and there were 4 males and 5 females. Their mean operation time was 117.7 ± 47.7 min and mean blood loss during the operation was 2.0 ± 2.4 mL. There were no significant differences between the day case LC performed group (41 patients) and the day case LC failed group (9 patients) (Table 1).

In 19 patients of the overnight stay LC group, 12 patients were discharged on the next day after the operation. Their mean age was 57.9 ± 12.8 years with a range of 37-76 and there were 5 males and 7 females. Their mean operation time was 100.3 ± 42.9 min and mean blood loss during the operation was 10.9 ± 22.5 mL. Another 7 patients had to remain in hospital for 3.1 ± 2.1 nights. The reasons for 5 for 2 nights admission were patient's request, that for another 1 for 4 nights admission was nausea and vomiting, and that for the other 1 for 8 nights admission was requirement of clinical observation following drain insertion due to bile spill (Table 2). Their mean age was 70.9 ± 12.8 years with a range of 56-80 and there were 4 males and 3 females. Their mean operation time was 119.4 ± 31.5 min and mean blood loss during the operation was 16.1 ± 17.6 mL. There were no significant differences in gender, operation time and blood loss but age (P < 0.05) between the one night stay LC group (12 patients) and the more nights stay LC group (7 patients) was significant (Table 1).

When the day case LC performed group and the one night stay LC group were compared, there were no significant differences between the groups.

The proportion of patients requiring unexpected or prolonged hospital stay was 7 out of 50 (14.0%) in the day case LC group compared with 2 of 19 (10.5%) in the overnight stay LC group when patient's request was excluded; thus 86.0% of patients in the day case LC group and 89.5% in the overnight stay LC group were discharged on the day of surgery or on the following day according to the schedule, respectively. There were no significant differences between the groups.

DISCUSSION

Although day case LC can save costs[3,9], concerns remain about patient safety. The morbidity of LC has been reported to be 4%-20%[12]. It is reported that about 50% of all complications during LC occur at the set-up of the pneumoperitoneum[13]. Typical mishaps at the set-up pe-

riod are bleeding from trocar sites and vascular injury[13]. Other complications include bleeding from the liver bed, spillage of gallstones or bile, bowel injuries and so on.

It has been recommended that patients should be observed for at least 24 h so that an intervention can be performed quickly if major complications such as bleeding or bile duct injury occur[14]. The incidence of major complications is substantially low. Arterial bleeding or hemorrhage generally becomes symptomatic during operation or within a few hours after surgery. On the other hand, bile duct injury becomes symptomatic during operation or several days after surgery.

In the present study, patients who underwent day case LC were observed for approximately 8 h after surgery. They had to meet MPADSS[11] before discharge was allowed. No difference in the number of postsurgical complications was found between the day case LC group and the overnight stay LC group and none of complications manifested during the hospital stay. These results imply that the hospital stay did not reduce the detection and subsequent consequences of complications. Therefore, 8 h of observation after LC appears to be sufficient. Several studies have also demonstrated the safety of LC with discharge on the same day[15].

In the present study, the vast majority of patients in both the day case LC group and the overnight stay LC group were successfully discharged and the proportion of people with unexpected or prolonged hospital stay was similar in both groups when patient's request was excluded. In addition, the duration of any unexpected or prolonged hospitalization was similar between the groups, suggesting that the severity of the causative condition was neither increased nor reduced by an overnight stay. These results demonstrate that in patients with an overnight stay, there are many patients who can have a day case LC safely.

It is important to identify risk factors for admission preoperatively to avoid the disappointment and disruption of an unexpected admission. The present study demonstrated that LC can be performed in selected patients as a day case procedure without jeopardizing the safety of the patients. The absence of readmission indicates that the criteria in this study are appropriate and strict. A previous diagnosis of acute cholecystitis or biliary pancreatitis was reported to be a highly predictive factor of hospital admission and patients with ASA grade of more than Ⅱ were more likely to require a postoperative stay of over 12 h[16].

The only difference between the day case and overnight LC group was age. Age was also the only difference between the one night stay and more nights stay group. The mean age was gradually higher from day case to more nights stay as hospital stay became longer. This result demonstrates that elderly patients show a tendency to like to stay in hospital rather than be a day case. This is unique in Japan and has not been reported from any other countries. Maggiore[7] reported that being 75 or older is a relative contraindication that led to exclusion in his criteria of patient selection. Some selection criteria for day case LC excludes patients older than 70 years[17,18]. Of course, these exclusion criteria are derived from the fact that elderly patients have a high risk of postoperative complications. Not only so, elderly patients in Japan are likely to stay hospital longer after LC probably because the hospital cost is relatively lower in Japan and their anxiety due to fear of suffering complications and pain at home is strong. Therefore, we must take special care to give elderly patients adequate information before surgery and a support system after discharge.

Adequate pain relief is essential in day case surgery. Various methods, such as peritoneal instillation of local anesthetic agents[19,20] and wound infiltration with local anesthetic agents[21], have been attempted to decrease postoperative pain. But Hilvering *et al*[22] reported the opposite result, that combined subcutaneous and intraperitoneal administration of levobupivacaine did not influence postoperative abdominal pain after LC. We innovated the TAP block as a postoperative pain block[10] and after that no patients complained of postoperative pain.

Postoperative nausea and vomiting are other factors that may influence postoperative discharge and hospital stay[23]. In this study, the most common reasons for unexpected or prolonged hospital stay were nausea and vomiting. Nearly half of unexpected or prolonged hospital stay patients in both day case and overnight LC groups were due to nausea and vomiting. Hereafter, an effective protocol for control of nausea and vomiting is an essential component in the day case LC service. The routine use of prophylactic anti-emetic agents such as ondansetron[5] and preemptive analgesia with non-steroidal anti-inflammatory drugs[24] may reduce the incidence of postoperative nausea and vomiting.

COMMENTS

Background

Laparoscopic cholecystectomy (LC) is a popular procedure in Japan. This surgery has been performed as an inpatient surgery, while it has been done regularly as ambulatory surgery in patients with uncomplicated gallstone disease in the United States and parts of Europe. On the other hand, ambulatory LC is performed in one hospital by day case, while in another hospital by overnight stay.

Research frontiers

In this study, the authors attempted to evaluate the applicability and safety of the ambulatory LC and to compare day case and overnight stay LC.

Innovations and breakthroughs

In this study, the authors demonstrate that day case LC can be performed safely with a low rate of complications and no readmissions and that most of the patients with an overnight stay LC can be performed safely as a day case. They also indicate the application and discharge criteria for ambulatory LC.

Applications

This study may represent a future strategy for LC as a day case procedure.

Peer review

The authors studied the applicability and safety of the ambulatory LC and the comparison between a day case and overnight stay procedure. It revealed that ambulatory LC can be performed as a day case procedure, according to the criteria as described in this manuscript, and that elderly patients need special care to reduce their anxiety due to the fear of suffering complications and pain after discharge. The results are interesting and may represent a future strategy for LC as a day case procedure.

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CASE REPORT

Evaluation of salvage surgery for type 4 gastric cancer

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Abstract

Patients with type 4 gastric cancer and peritoneal metastasis respond better to chemotherapy than surgery. In particular, patients without gastric stenosis who can consume a meal usually experience better quality of life (QOL). However, some patients with unsuccessful chemotherapy are unable to consume a meal because of gastric stenosis and obstruction. These patients ultimately require salvage surgery to enable them to consume food normally. We evaluated the outcomes of salvage total gastrectomy after chemotherapy in four patients with gastric stenosis. We determined clinical outcomes of four patients who underwent total gastrectomy as salvage surgery. Outcomes were time from chemotherapy to death and QOL, which was assessed using the Support Team Assessment Schedule-Japanese version (STAS-J). Three of the patients received combination chemotherapy [tegafur, gimestat and otastat potassium (TS-1); cisplatin]. Two of these patients underwent salvage chemotherapy after 12 and 4 mo of chemotherapy. Following surgery, they could consume food adequately and their STAS-J scores improved, so their treatments were continued. The third patient underwent salvage surgery after 7 mo of chemotherapy. This patient was unable to consume food adequately after surgery and developed surgical complications. His clinical outcomes at 3 mo were very poor. The fourth patient received combination chemotherapy (TS-1 and irinotecan hydrochloride) for 6 mo and then underwent received salvage surgery. After surgery, he could consume food adequately and his STAS-J score improved, so his treatment was continued. After the surgery, he enjoyed his life for 16 mo. Of four patients who received salvage total gastrectomy after unsuccessful chemotherapy, the QOL improved in three patients, but not in the other patient. Salvage surgery improves QOL in most patients, but some patients develop surgical complications that prevent improvements in QOL. If salvage surgery is indicated, the surgeon and/or oncologist must provide the patient with a clear explanation of the purpose of surgery, as well as the possible risks and benefits to allow the patient to reach an informed decision on whether to consent to the procedure.

Key words: Type 4 gastric cancer; Quality of life; Salvage surgery; Support Team Assessment Schedule-Japanese version; Palliative care; Systemic chemotherapy; Gastric stenosis

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INTRODUCTION

Patients with type 4 gastric cancer generally have a worse prognosis compared with patients with other types of advanced gastric cancer. This is primarily because of the high incidence of peritoneal metastasis in type 4 gastric cancer, which causes intestinal obstruction, hydronephrosis, or obstructive jaundice. Surgical treatment is often only palliative, and systematic chemotherapy is usually essential important to prolong survival[1-3]. In particular, patients who can consume food without gastric or intestinal obstruction often report better quality of life (QOL) during systemic chemotherapy. For gastric cancer, systemic chemotherapy with tegafur, gimestat and otastat potassium (TS-1) achieved higher response rates than conventional 5-flurouridine (5-FU)-based regimens in patients with poorly differentiated adenocarcinoma. Additionally, TS-1 alone or in combination with cisplatin, paclitaxel, or irinotecan, for example, achieved greater antitumor effects and longer survival time for gastric linitis plastica compared with conventional 5-FU regimens[1-3].

For esophageal cancer, salvage surgery is the only curative treatment option after definitive chemoradiotherapy[4]. By contrast, in gastric cancer treatment, if neoadjuvant chemotherapy is effective for primary non-curative gastric cancer, salvage surgery may be performed to evaluate the pathological outcomes. Outcomes of interest in previous studies were procedure-related morbidity, mortality, and survival, but not QOL[5]. It is important to evaluate the outcomes of non-curative surgery, and to understand the potential risks and benefits of non-curative surgery in patients with type 4 gastric cancer. This is particularly true for patients with unsuccessful chemotherapy who cannot adequately consume food because of gastric and intestinal obstruction. Such patients often require salvage surgery to allow them to consume food adequately. Here, we examined the impact of salvage surgery on QOL in four patients who were unsuccessfully treated with chemotherapy.

CASE REPORT

Patients

We identified four patients who could not consume food because of gastric stenosis and obstruction that occurred sometime after starting systemic chemotherapy. The patients were given information about the risk and benefit of salvage surgery, and underwent this procedure.

Procedures

The relationship between QOL and salvage surgery was analyzed. We evaluated QOL during chemotherapy, from the first cycle of chemotherapy until death, using the Support Team Assessment Schedule-Japanese version (STAS-J). The STAS-J records performance status, appetite loss, nausea, vomiting, diarrhea, constipation, oral mucositis, alopecia, and numbness, to provide outcome measures assessing quality of palliative care. Each item and the need for improvement is scored on a 5-point (0-4) scale, where high scores indicate many problems and low scores indicate few problems. For example, a score of 0 indicates no symptoms. A score of 1 indicates an occasional or minor single symptom that the patient does not think needs to be resolved. A score of 2 indicates moderate distress, occasional bad days, and symptoms limiting some activities within the extent of the disease. A score of 3 indicates a severe symptom that is often present and greatly affects the patient's activities and concentration. A score of 4 indicates a severe and continuous overwhelming symptom that prevents the patient from thinking of other things[6-8].

Table 1 Summary of the patients who underwent salvage surgery after chemotherapy

Three cases: Chemotherapy (TS-1 and CDDP)
Case 1: Salvage surgery was performed after chemotherapy about 12 mo, he could take a meal and improved QOL about 6 mo
Case 2: Salvage surgery was performed after chemotherapy about 7 mo, but he could not take a meal and improved QOL
Case 3: Salvage surgery was performed after chemotherapy about 4 mo, he could take a meal and improved QOL about 8 mo
One case: Chemotherapy (TS-1and CPT11)
Case 4: Salvage surgery was performed after chemotherapy about 6 mo, he could take a meal and improved QOL about 16 mo

TS-1: Tegafur, gimestat and otastat potassium; CDDP: Cisplatin; QOL: Quality of life; CPT11: Irinotecan.

Case reports

Three patients received TS-1 and cisplatin combination chemotherapy (Cases 1-3) and one received TS-1 and irinotecan combination chemotherapy (Case 4).

Case 1: This was a 68-year-old man. After 12 mo of chemotherapy, the patient was diagnosed with gastric stenosis caused by type 4 gastric cancer. His STAS-J scores for appetite loss and nausea increased because of gastric stenosis, indicating worsening of QOL (Figure 1A). Therefore, the patient underwent salvage surgery to improve his QOL. After salvage surgery, the patient could consume food adequately and his STAS-J scores improved. Chemotherapy was continued for a further 6 mo (Table 1 and Figure 1A).

Case 2: This was a 61-year-old man. This patient had gastric stenosis caused by type 4 gastric cancer before starting neoadjuvant chemotherapy (Figure 2A). However, as he could consume food adequately, he received combination chemotherapy. After 7 mo of chemotherapy, his gastric stenosis deteriorated (Figure 2B), which resulted in increases in STAS-J scores for appetite loss, nausea, vomiting, and performance status, thus worsening his QOL (Figure 1B). Therefore, this patient underwent total gastrectomy. However, this patient developed surgical complications and was unable to consume food adequately. The patient had a poor clinical course and died 3 mo after surgery (Table 1 and Figure 1B).

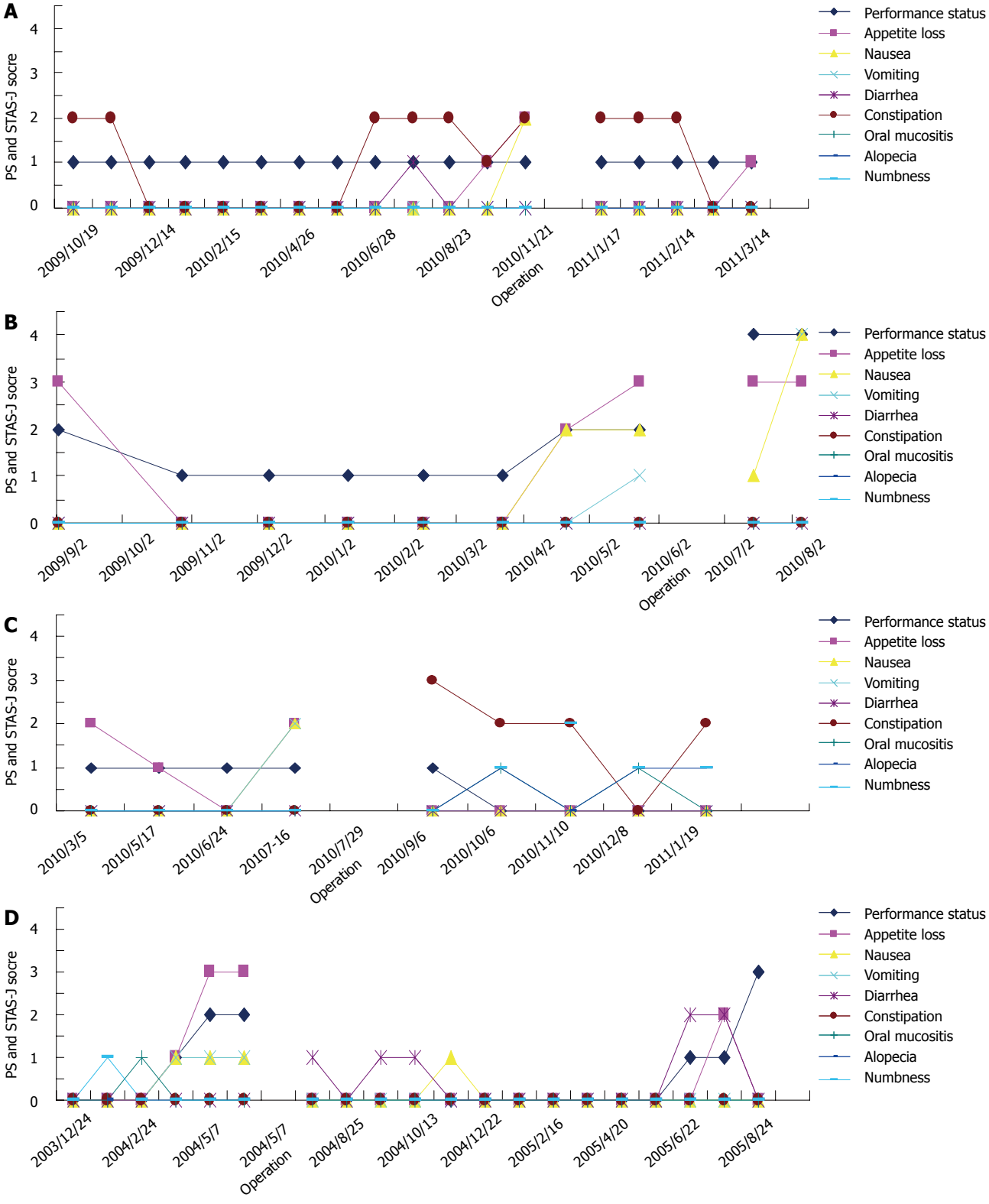

Figure 1 Clinical course of the four cases. A: Clinical course of Case 1; B: Clinical course of Case 2; C: Clinical course of Case 3; D: Clinical course of Case 4. STAS-J: Support Team Assessment Schedule-Japanese version

Case 3: This was a 69-year-old man. After 4 mo of chemotherapy, the patient was diagnosed with gastric stenosis caused by type 4 gastric cancer. His STAS-J scores for appetite loss and nausea increased, and his QOL worsened (Figure 3C). Therefore, the patient underwent total gastrectomy. After salvage surgery, his STAS-J scores improved and chemotherapy was continued for a further 8 mo (Table 1 and Figure 1C).

Case 4: This was a 30-year-old man who received TS-1 and irinotecan combination chemotherapy (Figure 3A and C) After 6 mo of chemotherapy, he was diagnosed

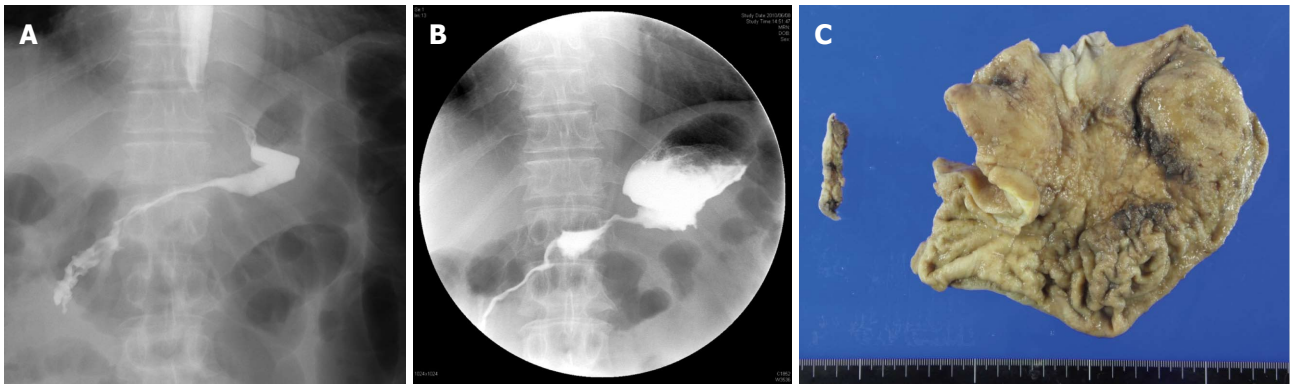

Figure 2 Images of Case 2. A: Gastrointestinal image before neoadjuvant Chemotherapy Figure; B: Gastrointestinal image after neoadjuvant Chemotherapy; C: Resected stomach.

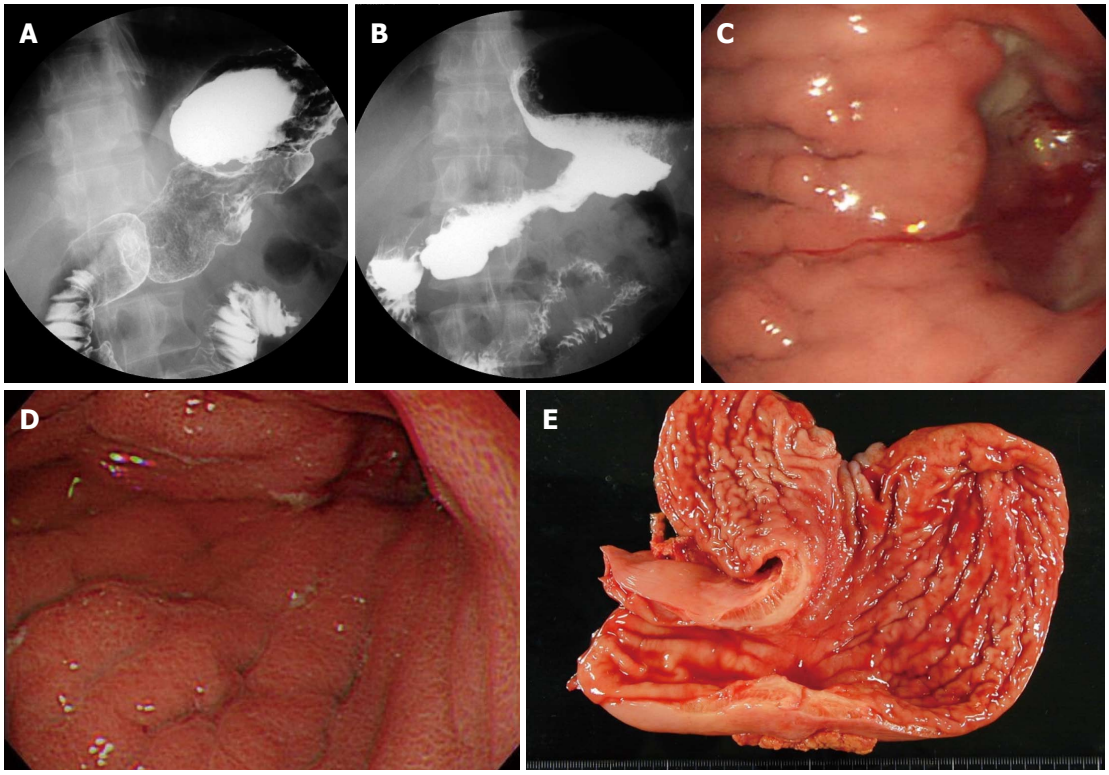

Figure 3 Images of Case 4. A: Gastrointestinal image before neoadjuvant Chemotherapy; B: Gastrointestinal image after neoadjuvant chemotherapy; C: Finding of gastrointestinal scope before neoadjuvant chemotherapy; D: Finding of gastrointestinal scope after neoadjuvant chemotherapy; E: Resected stomach.

with gastric stenosis caused by type 4 gastric cancer (Figure 3B and D). His STAS-J scores for appetite loss, nausea, vomiting, and performance status increased and his QOL worsened because of the gastric stenosis (Figure 1D). Therefore, the patient underwent salvage surgery. After surgery, the patient could consume food adequately and his STAS-J scores improved, so chemotherapy was continued. He enjoyed a good life for 16 mo (Table 1 and Figure 1D).

DISCUSSION

According to the S-1 plus cisplatin *vs* S-1 in randomized controlled trial in the treatment for stomach cancer (SPIRITS) trial the median overall survival (OS) was significantly longer in patients treated with S-1 plus cisplatin [13.0 mo (range: 7.6-21.9 mo)] than in those treated with S-1 alone (11.0 mo; 95% CI: 5.6-19.8 mo; hazard ratio for death, 0.77; 95% CI: 0.61-0.98; $P = 0.04$). Progression-free survival (PFS) was also significantly longer in patients treated with S-1 plus cisplatin than in those treated with S-1 alone [median PFS: 6.0 mo (range: 3.3-12.9 mo) *vs* 4.0 mo (range: 2.1-6.8 mo); $P < 0.0001$]. The PFS for cases 1, 2, 3 and 4 was approximately 12, 7, 4 and 6 mo, respectively, with a range of 3.3-12.9 mo, while the survival times were approximately 18, 10, 12 and 22 mo, respectively. Thus, the survival time of these patients was within the range reported in the SPIRITS trial, and the OS of our patients was not inferior to that in the SPIRITS trial. Unfortunately, effects of these treatments on QOL were

not reported in the SPIRITS trial, so we cannot compare QOL outcomes between our patients and those included in the SPIRITS trial[9].

Symptom relief should be the primary focus of palliative treatment, as recommended by the World Health Organization. Evaluating the effectiveness of palliative interventions should incorporate this goal and include QOL outcome assessments. We have found no articles reporting true QOL outcomes using reliable, validated QOL instruments in surgically managed patients with advanced gastric cancer[10,11]. The STAS includes items that assess the quality of palliative care. This instrument has been used in a variety of clinical fields to evaluate the quality of care or interventions, assess the prevalence of symptoms, and implement outcome measures in clinical practice. Here, we used the STAS-J to evaluate the effects of salvage surgery in patients with type 4 gastric cancer on performance status, appetite loss, nausea, vomiting, diarrhea, constipation, oral mucositis, alopecia, and numbness[6-8]. Type 4 gastric cancer often spreads from the upper to the lower body of the stomach through the submucosa, muscularis propria, and subserosa. Although gastro-jejunostomy is often performed to allow patients with type 4 gastric cancer and gastric stenosis or obstruction to consume food, it does not necessarily improve QOL. It is necessary to assess the impact of enteral nutrition caused by jejunostomy with that of salvage total gastrectomy on QOL. Surgical procedures, including total gastrectomy, gastro-jejunostomy, and jejunostomy, are associated with greater risk of complications than other medical assessments. Therefore, surgical management, including total gastrectomy, should be performed for patients in expectation of prolonged survival. Total gastrectomy as salvage surgery carries much greater risk than other palliative surgical procedures. Nevertheless, the QOL of three patients (Cases 1, 3 and 4) improved following salvage surgery. However, Case 2 did not experience an improvement in QOL; this patient had severe gastric stenosis and a greater number of peritoneal metastases compared with the other patients, and was unable to consume food after salvage surgery. It is difficult to improve the QOL of patients with severe stenosis and peritoneal metastasis the around stomach. Consequently, it is necessary to evaluate the risks and benefits of such salvage therapy, and it is essential that the patient is given an adequate description of the purpose of the surgery and the possible risks and benefits. Salvage surgery should only be performed once the patient has given appropriate consent.

There are few reports describing the QOL of surgically managed patients with gastric cancer. Such patients exhibit various clinical states, including peritoneal metastasis grade, presence/absence of invasion to adjacent structures, and general clinical conditions. In additional, the limitations and quality of salvage surgery differ substantially among hospitals. Therefore, it is difficult to precisely evaluate the impact of salvage surgery. Prospectively designed studies using credible QOL instruments are necessary to provide information with better information about the treatment and its outcomes, and thus facilitate the decision-making process.

Of four patients who underwent salvage total gastrectomy following unsuccessful chemotherapy, QOL improved in three but not in one. Salvage surgery can improve the QOL of most patients, but surgical complication and other issues may prevent improvements in QOL. Once indicated, it is essential that the oncologist/surgeon provides the patient with a detailed description of the purpose of surgery, as well as its potential risks and benefits, to allow the patient to reach an informed decision on whether to undergo salvage surgery.

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Events Calendar 2012

January 19-21, 2012
Gastrointestinal Cancers Symposium 2012
San Francisco, CA, United States

January 25-29, 2012
Alpine Liver and Pancreatic Surgery Meeting
Carlo Magno Zeledria Hotel,
Madonna di Campiglio, Italy

February 1-4, 2012
Society Of Laparoendoscopic Surgeons AsianAmerican Multi-Specialty Summit 2012 (SLS 2012)
Honolulu, HI, United States

February 4, 2012
Radio ENT 2012
Bangalore, India

February 14-16, 2012
7th Annual Academic Surgical Conference
Las Vegas, NV, United States

February 22-24, 2012
BTS 15th Annual Congress
Glasgow, United Kingdom

February 20-25, 2012
Minimally Invasive Surgery Symposium 2012
The Grand America Hotel,
Salt Lake City, UT, United States

March 7-10, 2012
Society of American Gastrointestinal and Endoscopic Surgeons Annual Meeting 2012 (SAGES 2012)
The San Diego Convention Center,
San Diego, CA, United States

March 9-10, 2012
Kieler Arthroskopiekurs Kniegelenk
Kiel, Germany

March 29- April 1, 2012
Endovienna 2012 - 5th World Congress for Endoscopic Surgery of the Brain Skull Base & Spine combined with The First Global Update on Fess, The Sinuses & The Nose
Vienna, Austria

March 7-11, 2012
American Hepato-Pancreato Biliary Association Annual Meeting 2012 (AHPBA 2012)
Eden Roc Resort, 4525 Collins Avenue,
Miami Beach, FL, United States

May 19-22, 2012
The 2012 Digestive Disease Week
San Diego, CA, United States

May 18-19, 2012
The American Pancreas Club Scientific Meeting
San Diego, CA, United States

June 1-5, 2012
48th American Society of Clinical Oncology Annual Meeting
Chicago, IL, United States

June 17-20, 2012
Digestive Disorders Federation Conference - Combined meeting of BSG, AUGIS, BAPEN & BSL
Liverpool, United Kingdom

June 20-23, 2012
44th meeting of European Pancreatic Club
Prague, Czech Republic

June 27-30, 2011
ESMO 14th World Congress on Gastrointestinal Cancer
Barcelona, Spain

July 1-5, 2012
10th World Congress of the International Hepato-Pancreato-Biliary Association joined with the European HPBA Congress
Paris, France

September 15-16, 2012
Current problems of gastroenterology and abdominal Surgery
Kiev, Ukraine

September 19-21, 2012
32nd Congress of the European Society of Surgical Oncology (ESSO)
Valencia, Spain

September 28 - October 2, 2012
37th European Society for Medical Oncology (ESMO) Congress
Vienna, Austria

November 4-7, 2012
8th National Cancer Research Institute Conference
Liverpool, United Kingdom

November 14-16, 2012
Pancreatic Society of Great Britain and Ireland Meeting 2012
Cameron House Hotel, Glasgow

December 8, 2012
IASGO 2012 - 22nd World Congress of the International Association of Surgeons, Gastroenterologists and Oncologists
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GENERAL INFORMATION

World Journal of Gastrointestinal Surgery (*World J Gastrointest Surg*, *WJGS*, online ISSN 1948-9366, DOI: 10.4240), is a monthly, open-access (OA), peer-reviewed journal supported by an editorial board of 336 experts in gastrointestinal surgery from 35 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

Maximization of personal benefits

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJGS* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article *via* online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJGS* is an OA journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJGS* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

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The major task of *WJGS* is to rapidly report the most recent results in basic and clinical research on gastrointestinal surgery, specifically including micro-invasive surgery, laparoscopy, hepatic surgery, biliary surgery, pancreatic surgery, splenic surgery, surgical nutrition, portal hypertension, as well as the associated subjects such as epidemiology, cancer research, biomarkers, prevention, pathology, radiology, genetics, genomics, proteomics, pharmacology, pharmacokinetics, pharmacogenetics, molecular biology, clinical trials, diagnosis and therapeutics and multimodality treatment. Emphasis is placed on original research articles and clinical case reports. This journal will also provide balanced, extensive and timely review articles on selected topics.

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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