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Neoadjuvant chemotherapy for locally advanced gastric cancer: With or without radiation

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postoperative complications. As few data are available in Japan and Korea, interpretation and implementation of neoadjuvant radiation or chemoradiation should be done with caution.

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Abstract

The role of perioperative chemotherapy for gastric cancer has been established for gastric cancers in their advanced stage. In most parts of the world, even in Japan and Korea, local recurrence of gastric cancer following curative resection remains a problem. Should radiation be added to chemotherapy to achieve better local and regional control? What is the current evidence? What are the concerns regarding neoadjuvant chemoradiation in terms of safety, efficacy and survival benefit? After a serious review of the literature, the authors conclude that it is still too early to get a definitive answer but radiation seems promising. It may bring a higher pathological response rate. Rationally, more high level clinical trials are needed to confirm the role of radiotherapy in the neoadjuvant setting or to ascertain subsets of patients who may benefit from it. It is of note that surgeons should pay attention to possible complicated circumstances following radiotherapy, maintain proper nutrition status and minimize the occurrence of

INTRODUCTION

Early detection of gastric cancer is not easily available worldwide except for in some countries such as Japan and Korea and some ongoing screening programs in areas with a high incidence of gastric cancer^[1]. Therefore, locally advanced gastric cancers, usually stage II-III cancers, predominate, which are vulnerable to local/regional recurrence and distant metastasis^[2-4]. That is the rationale for neoadjuvant chemotherapy and/or radiation. Downsizing the tumor to facilitate further resection, control of latent lymphatic and hematological micrometastasis and *in vivo* chemosensitivity assay to avoid unnecessary side effects of ineffective adjuvant chemotherapy may have theoretical benefits^[2]. The MAGIC trial^[5], which introduces perioperative chemotherapy into guidelines on gastric cancer, did not take an efficacy assessment of preoperative chemotherapy into consideration, compromising the chemosensitivity advantage of preoperative

chemotherapy. Increasing controversies have come out about the encouraging result from the MD Anderson Cancer Center, who reported a 30% pathological complete response (pCR) rate in a phase II single center clinical trial^[6].

Is neoadjuvant chemotherapy the best? Should we add radiation to the preoperative treatment for locally advanced gastric cancer? To gastric cancer located in either distal or proximal gastric cancer or just adenocarcinoma of gastroesophageal junction? What is the potential benefit and what are the potential additional surgical issues? The authors will address these issues.

IS NEOADJUVANT CHEMOTHERAPY THE BEST?

Small size, single arm, phase I and phase II studies of neoadjuvant chemotherapy on gastric cancer have been reported since the last century, usually with high toxic regimens such as etoposide, mitomycin, methotrexate and cisplatin^[3]. Neoadjuvant chemotherapy with different regimens, different routes, either regional or systemic, has been carried out widely since the emergence of novel antineoplastic regimens such as oxaliplatin, taxanes, irinotecan, fluoropyrimidines (capecitabine, S-1) and herceptin. The milestone study by Cunningham *et al.*^[5] found that perioperative chemotherapy significantly improved progression-free and overall survival in patients with operable gastric, gastroesophageal junction and lower esophageal lesions. The study, referred to as the MAGIC trial, with 503 patients enrolled, demonstrated that the hazard ratio for death and progression were 25% and 34% lower, respectively. However, we cannot find evidence supporting tumor shrinkage and downstaging by perioperative chemotherapy, as concluded by the study. No efficacy response evaluation, either radiographical or histological, has been reported yet. Inclusion of low esophageal lesions, which consisted of nearly 15% of the group, compromised its application in gastric cancer and gastroesophageal junction tumors.

Therefore, there is obviously an urgent need to identify patients who are actually non-responsive to preoperative chemotherapy to avoid useless adjuvant chemotherapy^[4,7-9]. Oncologists and surgeons are trying to improve the response rate, especially the pCR rate. One way is to find novel regimens, different combinations, and to incorporate radiation into the treatment modalities. European scholars changed the chemotherapy regimens from epirubicin, etoposide and cisplatin (EEP) to epirubicin, cisplatin and fluorouracil (ECF), and achieved a better pathological response rate^[10,11]. pCR rate is an ideal goal for neoadjuvant treatment. For breast cancer patients following neoadjuvant chemotherapy, pCR histology has been identified as an independent prognostic factor^[12,13]. Radiotherapy may be of help to achieve a higher pCR rate for gastric cancer^[14,15].

ADDITION OF RADIOTHERAPY IN NEO-ADJUVANT SETTING MAY BRING SURVIVAL BENEFIT

One recent systematic review and meta-analysis showed a statistically significant survival benefit with the addition of radiotherapy in patients with resectable gastric cancer, without subgroup analysis of pre-, intra- and post-operative radiotherapy^[16]. Even although the study confirmed radiotherapy as an armamentarium alternative, it cannot clarify the separate role of different types of radiotherapy, surgical procedures, especially lymphadenectomy, study design, sample size and inclusion criteria which differ remarkably^[17-24].

Whether the addition of radiation to the neoadjuvant setting is justifiable remains inconclusive. Skoropad *et al.*^[18] reported a randomized controlled trial evaluating preoperative radiotherapy (20 Gy/5 d) plus surgery and surgery alone. With 20 years follow-up, the study failed to demonstrate the survival benefit of radiotherapy but the median survival of the radiotherapy group was longer than the surgical group (28.8 mo *vs* 20.3 mo), as were the 5, 10 year survival rates (39% *vs* 30%; 32% *vs* 18%). Typical “L”-shaped curves were shown. The survival curve of radiotherapy continued to be above that of the surgical group until 15 years after randomization or later. This trend was also seen in gastric cancer patients with T3-4 or N positive lesions yet without intersection. They seem to be due to the decrease of loco-regional recurrences following R0 resection as well as suspicious intraoperative manipulative tumor cell dissemination. This may be the rationale supporting the role of radiotherapy. No data was available regarding the pattern of local and distant failures. Another randomized controlled study with a larger sample size did confirm the survival benefit in selected gastric cancer patients located in gastric cardia^[22]. With 370 randomized patients, it indicated a significant survival benefit for neoadjuvant radiotherapy compared with surgery alone (5 year survival rates, 30.1% versus 19.8%, respectively; $P = 0.0094$). The dosage in this study is 40 Gy compared to concentrated radiotherapy with 20 Gy in the above study. R0 resection was improved by radiotherapy (80% versus 62% for surgery alone; $P < 0.001$) without increasing morbidity and mortality. Better local control was also indicated (38.6% *vs* 51.7%, $P < 0.025$), regional lymph node metastasis 38.6% *vs* 54.6% ($P < 0.005$), yet distant metastasis was comparable (24.3% *vs* 24.7%).

The two studies illustrated above began in the 1970s, using 8-MV photon or telecobalt, now seldom used. Interesting results were from the first multi-institutional trial by Ajani *et al.*^[6] with only 32 patients enrolled from three institutions. Linear accelerators were used to deliver a dose of 45 Gy in 25 fractions of 1.8 Gy over 5 wk and the minimum energy allowed was 6 MV photons, with a preferred energy of ≥ 10 MV. Treatment consisted of two cycles of systemic 5-FU, LV and cisplatin followed

by chemoradiotherapy in the form of 45 Gy external beam radiotherapy (EBRT) with continuous infusion 5-FU. High pCR rate of 30% was reached as the primary endpoint. The median survival time for 33 patients was 33.7 mo with a median follow-up of 50 mo, while patients achieving a pCR or pPR had a significantly longer median survival time (63.9 mo). A recent phase III randomized German study incorporated photons into a linear accelerator with an energy no less than 5MeV, comparing preoperative chemotherapy with chemoradiotherapy for locally advanced adenocarcinoma of the esophagogastric junction^[25]. Patients with uT3-4NXM0 adenocarcinoma of lower esophagus and gastric cardia were randomized into two groups: induction chemotherapy with PLF followed by surgery; or chemotherapy followed by chemoradiotherapy followed by surgery. Unfortunately the study was closed prematurely due to low accrual. For the 119 eligible patients evaluated, the group with radiotherapy demonstrated a higher response rate (15.6% *vs* 2.0%). However, it did not translate into a significant 3 year survival benefit (27.7% *vs* 47.4%, *P*=0.07). The authors concluded that preoperative chemotherapy may improve survival and should be further investigated. Since patients with a pathological response can generally be translated into long term survival^[26,27] and even cure, to achieve a high response rate may be another goal in the management of gastric cancer. In all, more high level randomized controlled studies to address this issue are needed^[28].

One recent study from Japan^[29] with a small number of enrolled patients investigated the role of neoadjuvant chemoradiotherapy with S-1 and cisplatin (CDDP). The chemotherapy schedule included one cycle repeated after 6 wk. S-1 was administered orally every day on days 1-21 and CDDP was infused on days 1, 8 and 15. Radiation therapy was started concurrently with chemotherapy and repeated daily on days 1-5, 8-12, 15-19 and 22-26. A total of 10 patients were recruited. Seven patients underwent surgery and all had an R0 (no residual tumor) resection without surgical complications. The author concluded that neoadjuvant chemoradiotherapy with S-1 and CDDP may cause surgery to be delayed but shows promise for resectable advanced gastric cancer.

WHAT WILL WE DO TO ALLEVIATE SURGICAL CONCERNS FOLLOWING RADIATION?

Surgeons are always concerned about the safety and efficacy during the perioperative period and the timing of potential curative resection^[30,31]. It has been established that resection remains the main armamentarium; missing it may place gastric cancer patients with limited survival opportunities.

Radiation may lead to direct and indirect injuries. Ionizing radiation injures cells by transferring energy to critical biological macromolecules, including DNA, proteins and membrane lipids, which may also react with

high-energy free radical intermediates. Ultimately, free radicals produced may cause the same results. Pathological changes include edematous, thickened and hyperemic mucosal manifestation in the early stage, and fibrosis to a different extent in the late stage^[32,33]. Those micro and macro changes will certainly make normal surgical plates, especially those between draining lymph nodes and surrounding vasculatures. Of the most concern, the prepared anastomosis may be performed on radiated tissues. The fragile, edematous, hemorrhagic tissues may be easy to tear, making anastomotic leakage a nightmare for surgeons. Fortunately, the concern may not translate into clinical reality. One early study from May 1984 to July 1988 evaluated 67 patients treated with intraoperative radiation (IORT)^[18]. The most common nonfatal complication was anastomotic leak (*n* = 5). When compared with historical controls undergoing comparable surgery at this institution prior to the availability of IORT, complication rates were similar. The result has not yet been challenged within different controlled clinical trials. In the phase III German trial, only hospital mortality was reported, one in the chemotherapy group (1/49) and two in the chemoradiation group (2/45)^[25]. Median days on intensive care and total hospital stay did not differ (20 d *vs* 22 d), suggesting the anastomotic leakage rate may not be high. Even in a setting where both pre-operative and intraoperative radiotherapy were used, the rate of anastomotic leakage was only 2% (*n* = 1)^[19]. In the large randomized clinical trial by Zhang *et al*, there was also no statistical significant difference between two groups; 1.8% and 4% in radiation and surgery groups, respectively^[22]. Similar results have been obtained on neoadjuvant chemoradiotherapy for esophageal squamous carcinoma^[34,35].

Yet, surgeons should not be so optimistic about the rate of anastomotic leakage following radiotherapy as there are still hints from several studies^[30,31,36-41]. Necessary prophylactic measures should be taken for selected high risk patients, evaluated during or after surgery. In our experience, key points to prevent the occurrence of anastomotic leakage are to reduce the tension at the anastomotic site, make mucosa to mucosa anastomosis contact, avoid a tear in the muscular layer of the esophagus, especially when it is thin, retain necessary blood supply, and maintain drainage.

Anorexia, nausea and fatigue are almost ubiquitous problems during gastric radiation therapy. Nutritional and gastrointestinal support may be of great importance to complete the full course. Nearly 20% of patients may fail in completing planned radiation therapy. Malnutrition may in turn affect the safety and outcome of the surgery^[42]. Anastomotic leakage may be among the related complications. Other complications included late gastritis, uncomplicated gastric ulcers, or ulcers complicated by perforation and hemorrhage, acute pancreatitis and so on^[43].

FUTURE DIRECTIONS

Data on neoadjuvant radiotherapy for local and advanced gastric cancer are limited^[44]. Therefore, it is too early to

get a definitive answer. Rationally, we still have to investigate with high level clinical trials to confirm the role of radiotherapy in the neoadjuvant setting, to investigate different drugs as a radiosensitizer or as a combination, and to ascertain subsets of patients who may benefit^[45]. It is of note that surgeons should pay attention to possible complicated circumstances following radiotherapy, maintain proper nutrition status and minimize the occurrence of postoperative complications.

Of note, the limitation of this review is that few data from Japan and Korea are available regarding the role of radiotherapy for gastric cancer as radiotherapy is not widely accepted in those two countries, especially in the neoadjuvant setting. Surgical procedures with regional lymphadenectomy have been well standardized, leading to a much lower local recurrence rate. Ethnical differences among countries are still controversial. Whether neoadjuvant radiation could provide additional oncological benefit in Japanese or Korean patients, even in certain subgroups, is still waiting for more evidence. Clinical studies on neoadjuvant treatment should be based on the standardization of surgical procedures^[46] and sufficient sample size.

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S- Editor Wang JL L- Editor Roemmele A E- Editor Zhang DN

Dear readers,

In the February 2012 issue of the *World J Gastrointest Surg* (4(2):32-35) Scabini and Ferrando published an editorial entitled “Number of lymph nodes after neoadjuvant therapy for rectal cancer: how many are needed?” It has been brought to our attention that segments of the editorial are identical or closely resemble the essential parts of the discussion of the original article “Preoperative chemoradiotherapy does not necessarily reduce lymph node retrieval in rectal cancer specimens – Results from a prospective evaluation with extensive pathological work-up” that was published in the *Journal of Gastrointestinal Surgery* in 2009. Given the striking similarities of the two works, the *World J Gastrointest Surg* has decided to retract the editorial by Scabini and Ferrando.

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Long-term results of choledochoduodenostomy in benign biliary obstruction

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Abstract

AIM: To determine the long-term results of choledochoduodenostomy in patients with benign biliary obstruction.

METHODS: This prospective study was conducted at Sheri Kashmir Institute of Medical Sciences Srinagar Kashmir, India over a period of 10 years from January 1997 to December 2007. The total number of patients who underwent choledochoduodenostomy during this period was 270. On the basis of etiology of biliary tract obstruction, patients were divided into a calculus group, an oriental cholangiohepatitis group, a benign biliary stricture group and others. Patients were followed for a variable period of 13 mo to 15 years.

RESULTS: Choledochoduodenostomy (CDD) with duodenotomy was performed in four patients. CDD with removal of T- tube, CDD with left hepatic lobectomy and CDD with removal of intra biliary ruptured hydatid was performed in three patients each. In the remain-

ing patients only CDD was performed. Immediate post operative complications were seen in 63 (23%) patients, while long-term complications were seen in 28 (11%) patients, which were statistically significant. Three patients died during hospitalization while four patients died in the late post-operative period.

CONCLUSION: Our conclusion is that CDD is safe and produces good long term results when a permanent biliary drainage procedure is required.

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Key words: Choledochoduodenostomy; Oriental cholangiohepatitis; Biliary calculi; Cholangitis

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Malik AA, Rather SA, Bari SUL, Wani KA. Long-term results of choledochoduodenostomy in benign biliary obstruction. *World J Gastrointest Surg* 2012; 4(2): 36-40 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v4/i2/36.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v4.i2.36>

INTRODUCTION

Choledochoduodenostomy (CDD) has been the subject of considerable controversy since its first description by Riedel in 1892. Its acceptance is still debated in view of the expected complications, such as ascending cholangitis, sump syndrome and alkaline reflux gastritis. In spite of the good long-term results observed in some studies, CDD is considered a last resort for lower common bile duct (CBD) obstruction. The common indications for CDD have remained unchanged over the years and also have dominated our series. These are choledocholithiasis, lower bile duct strictures, worm obstruction, papillary or

ampullary stenosis, perivaterian diverticuli. In the modern era of endoscopy a significant number of patients still need surgical intervention for benign biliary duct obstruction but as repeated interventions on the CBD lead to increased morbidity and mortality, a permanent drainage procedure is indicated in all such patients. The present study was conducted to evaluate the effectiveness of CDD in preventing the need for repeated exploration and the occurrence of long-term complications.

MATERIALS AND METHODS

The prospective study was conducted at Sheri Kashmir Institute of Medical Sciences Srinagar Kashmir, India over a period of 10 years from January 1997 to December 2006, upon patients who underwent choledochoduodenostomy. The study comprised 270 patients (99 males and 171 females) of 20 to 70 years of age. Forty two patients were lost to follow up. The remaining 232 patients formed the database of this analysis.

All patients were subjected to baseline investigations which included haemogram kidney function tests, liver function tests and coagulogram. Abdominal sonography and endoscopic retrograde cholangiopancreatography (ERCP) were the most common investigation tools. Computerised tomography and magnetic resonance cholangiopancreatography were used when indicated. On the basis of pre-operative diagnosis and intra-operative findings, patients were divided into four groups (Table 1). These were the Calculus group where ERCP had failed to clear the common bile duct of stones, the Oriental cholangiohepatitis group (separately categorized because of different course of the disease process), the benign biliary Stricture group and the others (including cases of biliary ascariasis, intra-biliary rupture of hydatid liver, chronic pancreatitis, and portal hypertension with CBD stone.

Statistical analysis

Chi square test was used for statistical evaluation.

Technique of lateral choledochoduodenostomy

Side-to-side choledochoduodenostomy is the procedure of choice for all indications except iatrogenic injuries and the controversial indication of malignant obstruction. Complete circumferential division of the common bile duct or the common hepatic duct compromises the blood supply to both ends of the duct and may predispose the anastomosis to an ischemic stricture. After the cholecystectomy is carried out, the duodenum and pancreas are mobilized by an extensive Kocher manoeuvre. The common bile duct is exposed by incising the overlying peritoneum. The common bile duct is opened longitudinally with a scalpel at the supraduodenal location, extending proximally for 2 to 2.5 cm. Any manipulations such as removal of any stone, worms or biopsy are completed at this point. After common bile duct exploration and proper mobilization and exposure

Table 1 Final diagnosis in patients¹ (n = 270)

No.	Presentation	Male		Female		Total	
		n	%age	n	%age	n	%age
1	Calculus group	41	15.18	92	34.07	133	49.26
2	OCH group	39	14.44	42	15.55	81	30.00
3	B.B. Strictures/ligatures ²	9	03.33	17	06.29	26	09.63
4	Others	10	03.70	20	07.40	30	11.11
Total		99	36.66	171	63.33	270	100

¹More findings than one were present in many cases; ²This group also includes cases of ampullary stenosis.

have been achieved, a longitudinal incision is made in the post bulbar duodenum using cautery for a distance of approximately 1.5 cm. A single layer anastomosis using 3-0 Vicryl is accomplished by beginning posteriorly and positioning the knots on the outside of the anastomosis. The anterior portion of anastomosis is performed using simple interrupted sutures. A closed suction drain is placed in the area of anastomosis but not in direct contact with it. The drain is removed on the fourth post-operative day.

Follow up

The patients were followed up 6 weekly for first three months, quarterly for the following nine months, biannually for the next two years and annually thereafter.

Follow up was for an average period of 8.25 years (ranging from 13 mo to 13 years). During follow up visits investigations were guided by comprehensive history and clinical examination including liver function test, abdominal sonography, gastroduodenoscopy and biliary scintigraphy. Deworming of the patients was a final and important component of our follow up. The final outcome of the patients was recorded and systematically arranged for evaluation.

RESULTS

In our study of 270 patients there was not much difference in the mean ages of the patients of the two sexes: 47.12 ± 12.61 in males, 44.92 ± 13.83 in females ($P > 0.05$).

Among the clinical features, pain was the most consistent symptom in all cases (100%) followed by fever/rigors (50%), vomiting (43%), jaundice (33%). At the time of presentation 53.33% of the patients had serum bilirubin less than 1.3 mg%, and only 11.8% of the patients had levels above 10 mg%. Serum alkaline phosphatase was raised in 92.22% of the patients, and was normal in only 7.78%.

The size of CBD varied from 2 to 3 cm in our series. CDD with duodenotomy was required in 4 patients for impacted stones at the lower end of CBD. CDD with removal of T-tube, CDD with (L) Hepatic Lobectomy and CDD with Removal of intra-biliary ruptured hydatid was performed in three patients each. Redo-CDD was carried out in two patients, one each from oriental cholangiohepatitis (OCH) and Calculus groups, who had

Table 2 Post-operative complications in cases (*n* = 270) (%)

Complications	Calculus group	OCH group	Stricture group	Others group	Total	<i>P</i> value
Wound						
Infection	9 (6.76)	6 (7.4)	1 (3.84)	1 (3.33)	17 (6.2)	> 0.05
Dehiscence	-	-	-	1 (3.33)	1 (0.3)	> 0.05
Hernia	1 (0.7)	-	-	-	-	> 0.05
Post-op. fever	5 (3)	10 (12)	1 (3)	1 (3)	17 (6)	> 0.05
Septicaemia	-	4 (5)	1 (3)	2 (6)	7 (3)	> 0.05
Pulmonary						
Atelectasia	6 (4)	3 (3)	2 (7)	1 (3)	12 (4)	> 0.05
Pneumonia	1 (0.75)	2 (2)	-	-	3 (1)	> 0.05
Peritoneal						
Haemorrhage	-	-	-	-	-	
Bile drainage	1 (0.75)	2 (2)	1 (3)	-	4 (2)	> 0.05
Cardiovascular	-	-	-	-	-	
MI	-	-	-	-	-	
Arrhythmia	-	2 (2)	-	-	2 (0.74)	> 0.05
Total					63 (23.3)	NS

P value > 0.05 (non-significant). NS: Non-significant; OCH: Oriental cholangiohepatitis; MI: Myocardial infarction.

undergone CDD three and seven years earlier, respectively. Redo-CDD was performed in these patients, instead of CBD exploration only, because of the presence of distal stricture. The operative technique in redo-CDD was same as was used in other patients. All patients with OCH had undergone unsuccessful endoscopic treatment before surgery.

As shown in Table 2, 63 patients (23.33%) across all four groups developed immediate post-operative complications. This was statistically insignificant (*P* > 0.05). Long-term complications were seen in 28 (11%) patients (Table 3). No case of sump syndrome, recurrent/residual calculi or biliary ascariasis was recorded. On long-term follow up patients were classified on the basis of symptomatology and investigations of the four groups can be seen in Table 4.

As shown in Table 5, 3 patients died during their hospitalization, due to septicaemia and its complications in all cases. Four patients died in the late post-operative period, including 3 patients from the OCH group who had developed liver abscess on long-term follow up and died of the same. Thus the overall mortality was 2.59%.

DISCUSSION

The historical development of choledochoduodenostomy was summarized by Madden and associates in 1970. The review of the relevant literature and the observations of the present study suggest that the indications for CDD remain very much the same as those detailed by Degenshein^[1] in 1974 (except for the malignant ones). CDD has been recommended in the treatment of multiple calculi of the common bile duct, retained or residual stones, hepatic stones, distal common bile duct strictures, ampullary stenosis, benign ampullary tumours^[1], primary duct stones, recurrent common duct stones, dilated CBD with diameter greater than 20 mm, failure of ERCP, non-availability of ERCP^[2-6]. While CDD is

Table 3 Incidence of long-term complications (*n* = 225) (%)

Complications	Calculus group <i>n</i> = 106	OCH group <i>n</i> = 81	Stricture group <i>n</i> = 22	Others group <i>n</i> = 16	Total	<i>P</i> value
Alkaline gastritis	6 (5.67)	4 (5.4)	1 (4.5)	-	11 (4.88)	> 0.05
Cholangitis	-	5 (6.8)	1 (4.5)	1 (3.84)	7 (3)	> 0.05
Liver abscess	-	3 (3.7)	-	-	3 (1)	> 0.05
Stenosis of anastomosis	1 (0.96)	-	1 (4.5)	-	2 (0.8)	> 0.05

P value > 0.05 (non-significant). OCH: Oriental cholangiohepatitis.

particularly recommended for use in elderly patients^[7], it is also recommended in younger patients since a more aggressive therapy may be indicated in their often “more aggressive lithogenic diathesis”^[8]. Choledocholithiasis (primary/secondary, retained/residual, recurrent or impacted) remains the sole indication in our series (49.26%) and none of the patients developed recurrent or residual stones, making CDD highly recommendable for such patients. There are some patients where CDD is contraindicated. These include patients with CBD less than 15 mm in diameter, perivaterian diverticulum and sclerosing cholangitis.

OCH was the next most common indication for CDD in our series (30%, i.e., 81 patients). This was expected as our Institute is in a high prevalence zone of the disease. This poses a challenge to the surgeons to treat these cases effectively. We subjected 3 patients to CDD with left hepatic lobectomy for hepatolithiasis and atrophied lobe. In the remaining 78 patients CDD was performed after the stones and debris had been removed. Of these patients 10% developed solitary/multiple liver abscesses, probably by the development of new proximal strictures/stones making the draining anastomosis less efficient. Recently, Tang *et al.*^[9] used laproscopic choledochoduodenostomy (LCD) as an effective drainage procedure in 12 patients with recurrent pyogenic cholangitis. There was no recurrence of cholangitis or any evidence of sump syndrome in these patients.

The principal aim of this study was to analyze the results obtained with CDD in patients followed for 1-13 years and to determine the safety of this operation even at the extremes of age. We experienced 3 (1.11%) early post-operative deaths due to suppurative cholangitis or biliary peritonitis. There were 4 (1.77%) late deaths (between 8 mo to 10 years) during the long-term follow up. Although a mortality rate of less than 1% has been reported for CDD⁷, the average mortality rate is 2%-5% and can be much higher^[1,2,4,10]. The morbidity of CDD observed in our study (23.33%) as well as the type of observed complications, parallels those previously reported in the literature. Perhaps the most important aspect of our study is absence of sump syndrome and interestingly, biliary ascariasis. Sump syndrome is a rare and late complication of side-to-side CDD. Its prevalence has long remained uncertain and has been reported to vary between 0% and 9.6%^[4,8,11]. Based on our observations, three factors could explain the absence of this complication in our series in spite of side-to-side anastomosis being

Table 4 Clinical classification of the patients (n = 225)

Results	Patient complaint	Ultrasonography	Liver function test	EGD	HIDA scan	Total
Excellent	None	Normal	Normal	-	-	116 (51.55%)
Good	Occasionally dyspeptic	Normal	Normal	+/-	-	93 (41.33%)
Moderate	Evident dyspepsia, nausea, bilious vomiting or fever rigours	Normal or IHD dilated	Normal or slightly deranged	Alkaline gastritis	Patent anastomosis evidence of gastric reflux	11 (4.88%)
Bad	Septecemia/cholangitis, anastomotic stenosis	Liver abscesses	Grossly deranged	+/-	Patent anastomosis, dilated IHD with slow transit	5 (2.22%)

EGD: Esophagogastrroduodenoscopy; IHD: Intra-hepatic duct.

Table 5 Demographics, diagnosis and cause of death of 7 patients who died after choledochoduodenostomy

No.	Age (yr)	Sex	Time	Initial daignosis	Cause of death
1	55	M	1st POD	Suppurative cholangitis	Septic shock/DIC
2	32	F	2nd POD	Biliary peritonitis	Septicaemia with arrhythmia
3	65	M	12th POD	Infected liver hydatid with intra-biliary rupture	Wound dehiscence with septicaemia with ARDS
4	54	M	8 mo	OCH with right lobe liver abscess with cholangitis	Septicaemia with MODS
5	46	F	13 mo	OCH with multiple liver abscess	Septicaemia with MODS
6	58	F	15 mo	Suppurative cholangitis	Arrhythmia
7	45	M	10 yr	OCH with multiple liver abscess with sepsis	Septicaemia with MODS

OCH: Oriental cholangiohepatitis; MODS: Multiple organ dysfunction syndrome; DIC: Disseminated intravascular coagulation; ARDS: Acute respiratory distress syndrome.

used in all the cases. First, a sump with wide anastomosis provides effective drainage of food debris that enters the bile duct. Second, the lower aspect (sump) of the anastomosis is usually narrow and this prevents the entry and impaction of food debris in the sump segment. A third important factor was the pre-operative ERCP which was carried out in 89.25% of patients in which wide papillectomy was made in most cases, thereby arresting this complication before it occurred.

Our study was conducted in a zone of high endemic ascariasis in which the surgeons created a biliary-enteric anastomosis with an inherent risk of worm migration into the biliary radicals. To contain this risk the patients were advised to take regular antihelminthic drugs at intervals of 3-4 mo to keep their intestinal worm load to the minimum. Interestingly, even those patients who did not comply with this regime did not show any increased incidence of biliary ascariasis. This was probably because a wide gateway created allows the worms to pass easily in either direction without getting stuck, thus avoiding the pathogenesis of biliary ascariasis and its complications. However, further studies are needed to confirm this. On long-term follow up we observed alkaline reflux

gastritis in 4.88% of the patients. These patients were treated effectively by ursodeoxycholic acid (dose 300 mg BD for 10-14 d). Mihmanli *et al.*^[12] noticed a higher incidence of alkaline reflux gastritis in their series (20.8%). In our series of 225 patients the incidence of cholangitis observed was low, at 3.11%, (7 patients of whom 5 were from the OCH group), possibly explained by the progressive nature of the disease in the proximal hepatobiliary segments. Escudero-Fabre *et al.*^[13] reported proved cholangitis in 4.2% of cases. In the clinical classification of the patients, according to the results from the long-term analysis, the “Good” and “Excellent” were predominant, with 93 patients (41.33%) in the former group and 69 patients (30.66%) in the latter. The “Moderate” group of 48 patients (21.33%) included patients with evident dyspepsia, nausea, bilious vomiting (alkaline gastritis) or fever and rigors (cholangitis). We had 15 patients (6.66%) in the “Bad” category, all of whom had cholangitis/septicemia and liver abscess(es) and most of whom were from the OCH group. Mihmanli *et al.*^[12] observed 75% of CDD patients in excellent or good category and the remaining 25% in moderate category. Bhandarkar *et al.*^[14] observed that LCD is a safe and effective option in patients with stones in a dilated bile duct when endoscopic clearance has failed. Tang *et al.*^[9] selected twelve patients with diagnosis of recurrent pyogenic cholangitis with the absence of intrahepatic stricture for laparoscopic choledochoduodenostomy during the period from 1995 to 2002. The majority of patients had repeated attacks of cholangitis and had already undergone multiple sessions of endoscopic and operative lithotripsy. The laparoscopic choledochoduodenostomy was performed using a five-port approach with the patient lying in the supine position. The stones were first cleared through the longitudinal supraduodenal choledochotomy followed by construction of a side-to-side diamond-shaped anastomosis of at least 15 mm between the bile duct and the first part of the duodenum using 2/0 monocryl in the single-layer method. The median operation time was 137.5 min (90-270) and the median postoperative stay was 7.5 d (5-20 d). Average analgesic requirement post operation was 126 mg (50-200 mg) intramuscular pethidine. There was one postoperative bile leak, and this complication was resolved by conservative measures. Upon a mean follow up of 37.6 mo (6-91 mo), there was no recurrent attack of cholangitis or any evidence of

sump syndrome in this group of patients. The authors concluded that laparoscopic choledochoduodenostomy is a safe and effective drainage procedure for patients with RPC. Complications are uncommon and postoperative results are promising.

In conclusion, a number of inferences can be drawn from the observations made in this study. CDD produces, both in elderly high risk patients and in younger ones with a longer life expectancy, good long term results in the treatment of benign biliary tract obstruction when a permanent biliary drainage procedure is required. However, the size of the CBD is of critical importance and should be at least 15 mm in diameter. Meticulous and precise suturing techniques are also essential. If these precautions are observed, cholangitis and symptoms related to sump syndrome are absent or occur very infrequently. While CDD is not the ideal procedure for OCH patients who rather need a multidisciplinary approach, it is the operation of choice in benign biliary tract obstruction.

COMMENTS

Background

Choledochoduodenostomy (CDD) has been performed for a variety of diseases of the biliary tract and pancreas.

Research frontiers

CDD has been recommended in the treatment of multiple calculi of the common bile duct (CBD), retained or residual stones, hepatic stones, distal common bile duct strictures, ampullary stenosis, benign ampullary tumours: primary duct stones, recurrent common duct stones, dilated CBD with diameter more than 20 mm, failure of endoscopic retrograde cholangiopancreatography (ERCP), non-availability of ERCP. The principal aim of this study was to analyze the results obtained with CDD and to determine the safety of this operation even in the extremes of age.

Innovations and breakthroughs

While CDD is recommended as a treatment modality in elderly patients, it is also recommended in younger patients since a more aggressive therapy may be indicated in their often more aggressive lithogenic diathesis.

Applications

Although, sometimes replaced by endoscopic papillotomy or sphincterotomy, there remain situations where surgical therapy is required.

Peer review

The authors have conducted the present study to evaluate the effectiveness

of CDD in preventing the repeated exploration and occurrence of long-term complications in patients with common bile duct obstruction. The results are interesting and may form the basis of further study.

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Hybrid natural orifice transluminal endoscopic surgery for ileocecal resection

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Abstract

Although laparoscopic colectomy is commonly performed around the world, an operative wound formed during the surgery is large but not sufficient enough to convert for the majority of open surgery. Thus, a certain sized skin incision is required to remove the resected colon. Here we report the case of a pure laparoscopic ileocecal resection which involves transanal specimen extraction. We present a case characterized by a laterally spreading type of tumor of the cecum. We performed a pure laparoscopic ileocecal resection and the resected specimen was removed transanally using colonoscopy. Intracorporeal functional anastomosis was then performed using a flexible linear stapling device under supporting barbed suture traction. The patient was discharged without complications on postoperative day 4. Laparoscopic colectomy performed with minimal incision could essentially increase the usage of this surgical technique. Although our method is restricted to flat or small lesions, we think it is a feasible and realistic solution for minimization of operative invasion because it involves specimen extraction through a natural orifice.

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INTRODUCTION

Laparoscopic-assisted colon resection has been well described for multiple surgical indications. Recurrence rates of cancer after laparoscopically-assisted colectomy were similar to those after open colectomy, suggesting that laparoscopic surgery is an acceptable alternative to open surgery^[1]. However, this typically requires an abdominal incision for specimen removal, which is commonly associated with postoperative pain. The combination of standard laparoscopy and specimen extraction through a natural orifice has the potential to reduce wound-related complications. We describe the technical approach to laparoscopic ileocecal resection with transanal specimen extraction which avoids an abdominal wall large incision and may be considered as an alternative approach to conventional minimally invasive colectomy, even in patients with right sided flat or small colon lesions.

CASE REPORT

A 71-year old male with a history of chronic obstructive pulmonary disease and asthma complained of lower

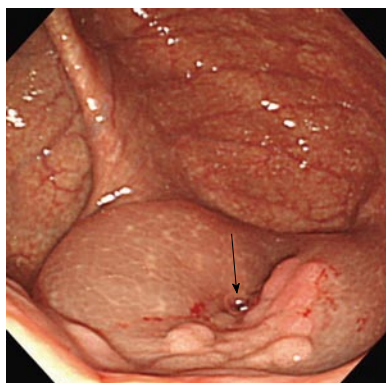


Figure 1 Lesion was beside the appendix orifice (arrow).



Figure 2 Resected specimen was extracted through the opened colectomy made at the ascending colon using snare forceps *via* colonoscopy through the anus.

abdominal pain, which was then explained as a symptom of benign prostate hyperplasia later that day. Colonoscopy revealed a laterally spreading tumor at the cecum that was unresectable by colonoscopy due to the size and location of the lesion. The lesion was 25 mm and was just beside the appendix orifice (Figure 1). We first injected normal saline into below the mucus membrane to try endoscopic submucosal dissection but we gave up resection due to technical difficulty. Pathology of the biopsied specimen showed borderline malignancy. Therefore, we proposed laparoscopic ileocecal resection.

A preoperative oral magnesium citrate bowel preparation was given. After induction of general anesthesia, the patient was placed in the lithotomy position. The colonoscope was inserted in to the cecum in advance. A 15-mm SILS port was placed just caudal to the umbilicus for the 30-degree, 5mm laparoscopy and the flexible forceps. One additional 5-mm trocar was placed in the right upper quadrant. First, the ileocolic artery was identified. A lymph node around the artery was dissected using laparoscopic coagulating shears (LCS) and the ileocolic artery and vein were transected after clamping them with a 5 mm clip. The right colon and ileum were mobilized. The mesocolon was dissected from the terminal ileum to ascending colon where we prepared the distal margin of resection. The level of distal bowel resection was de-



Figure 3 Intracorporeal laparoscopic full thickness V-Loc continuous suturing performed on the oral and anal open ends after side to side anastomosis by a linear stapler.



Figure 4 Post operative scars.

termined *via* intraoperative colonoscopy, the cecum and ascending colon were irrigated with iodine, and colonoscopy was also performed to ensure complete irrigation during operation. After clamping the laparoscopic bowel clip for the oral side of the cutting point of the terminal ileum, the lesion was transected using a LCS with adequate margins at the anal cut ends. The resected colon was retrieved using snare forceps *via* colonoscopy through the anus (Figure 2). Next, we made a temporary suture by using a barbed suture (V-Loc, Covidien) at both the oral and anal cut end of anti-mesenteric side of bowel. Then we made a side to side anastomosis with a flexible linear stapler under retraction of the stay suture. Succeeding, we made a continuous closure suture for both the oral and anal open edge (Figure 3). Then we cut out the suture line with the flexible linear stapler to make the intracorporeal functional end to end anastomosis. Finally, we made subcutaneous sutures for the two incisions (Figure 4).

Laparoscopic ileocecal resection was successfully performed using a natural orifice removal approach with two skin incisions. Operating time was 240 min and the estimated blood loss was 28 mL. The resected specimen was 8cm with a 25 mm sized lateral spreading tumor at the cecum. The pathological diagnosis was adenoma with borderline malignancy, the same as the preoperative diag-

nosis. The patient complained of minimal pain. Oral intake was tolerated on postoperative day 1 and the patient was discharged on postoperative day 4 without complications.

DISCUSSION

These days, even in the colon, endoscopic submucosal dissection is performed safely and reveals good outcomes for wide based lesions such as laterally spreading tumors or early colonic cancers^[2,3]. In this case, the lesion was just beside the appendix orifice. Therefore, we thought complete resection was impossible. We then proposed minimally invasive laparoscopic surgery for this patient. Laparoscopic surgery has increased dramatically around the world over the past 20 years and laparoscopic cholecystectomy has become a standard operation in the gall bladder. Furthermore, laparoscopic colectomy has shown favorable results^[4] compared with open surgery^[5-7]. However, it is still not considered a standard operation because the incision for removing the resected colon is large. In order to standardize laparoscopic colectomy, it is essential to minimize the incision. Therefore, although there is a transvaginal way^[8], removal of the resected colon through the anus is the most reasonable way to minimize the incision. Using the anus as a route for specimen colectomy extraction has been described extensively both in experimental and clinical settings^[9,10] and some reports describe a series of patients with left-sided malignancies who underwent successful laparoscopic sigmoidectomy and transanal specimen extraction, showing good oncological results^[11]. It is true that retrieving the specimen from the right side of colon is more difficult than the left. One report shows a right side single incision operation but the size of scar is 3cm and not pure laparoscopic surgery^[12]. A Medline search shows that there are no reports of transanal retrieval of the right side colon, except for the transvaginal route. If the lesion is small or flat, it is not impossible to pull out the lesion from the anus using colonoscopy. Whereas, restricted port, functional end to end anastomosis, which is one of the favorable intracorporeal laparoscopic anastomosis, is quite difficult. To solve this problem, we used two supportive sutures by a barbed suture (V-Loc). One is an anti-mesenteric side by side suture to protect from rotation and slipping out of the bowels from the linear stapler during side to side anastomosis. Another is a continuous closure suture for both the oral and anal open edge. Without this preparation suture before closing cut the colon by linear stapler, the closure of the colon may easily tend to be incomplete. The barbed suture is suitable for this procedure because this suture does not loosen the closed edge and does not require a suture tie. The linear cutter, a flexible equipment grasper, is also useful. In this operation there are some risks of infection due to opening the bowel in the abdominal cavity. To avoid stool leakage during the operation from the both oral and anal side of the colon, complete preparation was performed with iodine

during surgery under direct view using colonoscopy. We are already accustomed to similar hybrid natural orifice transluminal endoscopic surgery (NOTES) procedures^[13] and have also performed trans anal removal of the distal colon^[14,15]. On the other hand, the procedure requires a surgeon with advanced laparoscopic skills and the ability to perform intracorporeal suturing. However, improved skills of laparoscopic surgeons and robotic surgery may resolve these technical issues. Although transanal specimen extraction may not be possible in patients with a small caliber colon or large lesion, pure laparoscopic ileocecal resection is an applicable option for patients requiring elective ileocecal resection or right hemicolectomy and appears to be associated with little incisional pain and rapid recovery. Laparoscopic surgery involving NOTES procedures are still being developed. Therefore, our technique might be feasible as a pre-NOTES technique. More studies on this surgical technique in future will confirm its technical feasibility.

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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
Bangkok, Thailand



INSTRUCTIONS TO AUTHORS

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Acknowledgments

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Chinese journal article (list all authors and include the PMID where applicable)

- 2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

- 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

Organization as author

- 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.00000035706.28494.09]

Both personal authors and an organization as author

- 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]

No author given

- 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]

Volume with supplement

- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; **(401)**: 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

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

Books

Personal author(s)

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

Chapter in a book (list all authors)

- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

- 12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

- 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

Conference paper

- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

- 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

Statistical data

Write as mean \pm SD or mean \pm SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as

χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as *ν* (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, *m* (B) = 78 kg; blood pressure, *p* (B) = 16.2/12.3 kPa; incubation time, *t* (incubation) = 96 h; blood glucose concentration, *c* (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, *p* (CEA) = 8.6 $24.5 \mu\text{g/L}$; CO₂ volume fraction, 50 mL/L CO₂, not 5% CO₂; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantum numbers can be found at: http://www.wjgnet.com/1948-9366/g_info_20100312191949.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.

Genotypes: *gyrA*, *arg 1*, *c myc*, *c fos*, *etc.*

Restriction enzymes: *EcoRI*, *HindIII*, *BamHI*, *Kho I*, *Kpn I*, *etc.*

Biology: *H. pylori*, *E. coli*, *etc.*

Examples for paper writing

Editorial: http://www.wjgnet.com/1948-9366/g_info_20100312190249.htm

Frontier: http://www.wjgnet.com/1948-9366/g_info_20100312190321.htm

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