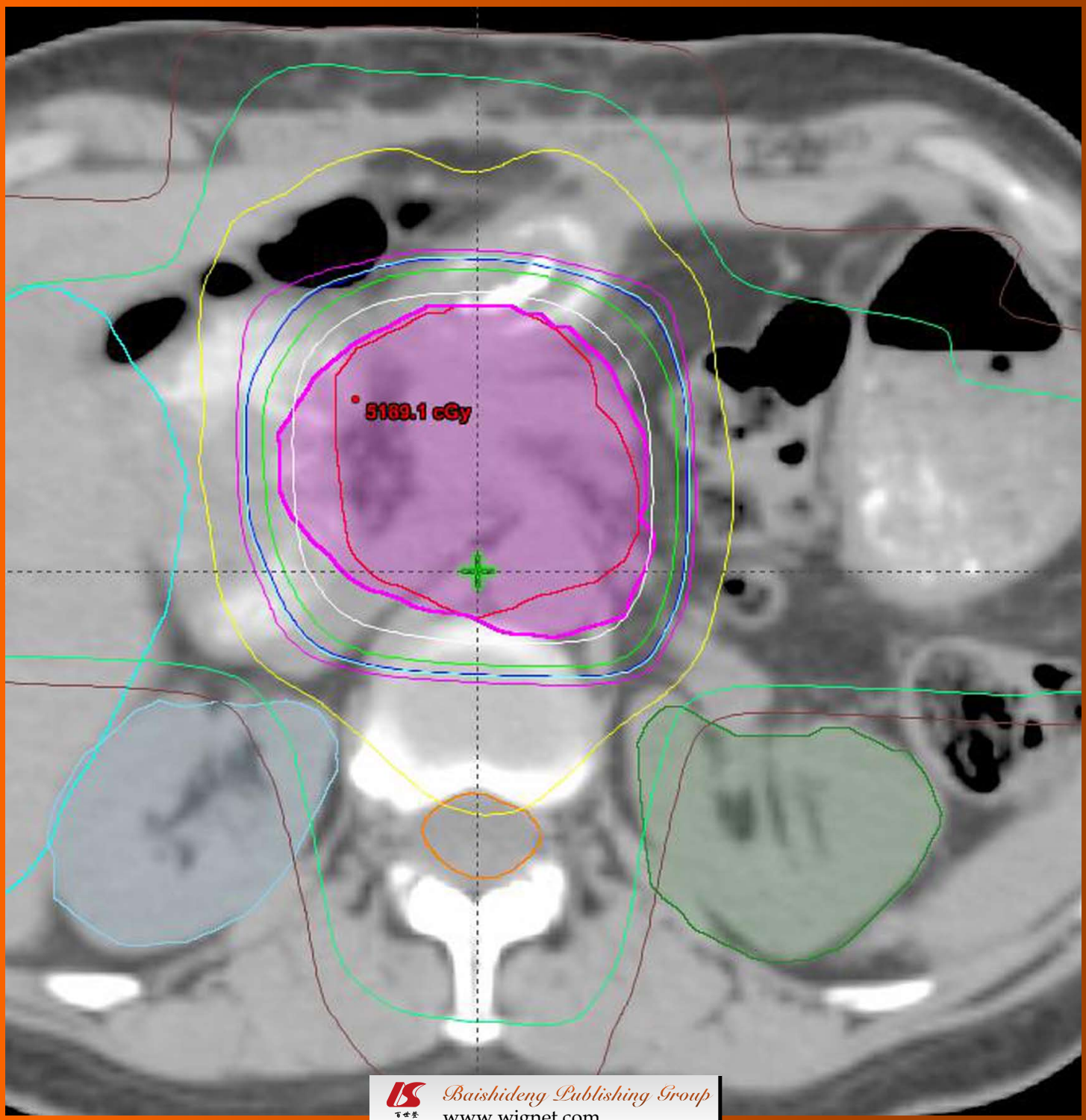
ISSN 1948-9366 (online)

World Journal of *Gastrointestinal Surgery*

World J Gastrointest Surg 2010 November 27; 2(11): 373-388



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World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 2 Number 11 November 27, 2010

EDITORIAL

373 Adjuvant chemoradiotherapy for resected pancreas cancer

Iott M, Neben-Wittich M, Quevedo JF, Miller RC

REVIEW

381 An ongoing dispute in the management of severe pancreatic fistula: Pancreatospleenectomy or not?

Dellaportas D, Tympa A, Nastos C, Psychogiou V, Karakatsanis A, Polydorou A, Fragulidis G, Vassiliou I, Smyrniotis V

CASE REPORT

385 Sporadic gastric carcinoid tumor successfully treated by two-stage laparoscopic surgery: A case report

Kinoshita T, Oshiro T, Urita T, Yoshida Y, Ooshiro M, Okazumi S, Katoh R, Sasai D, Hiruta N

World Journal of Gastrointestinal Surgery
Volume 2 Number 11 November 27, 2010

Contents

ACKNOWLEDGMENTS	I	Acknowledgments to reviewers of *World Journal of Gastrointestinal Surgery*
APPENDIX	I	Meetings
	I-V	Instructions to authors
ABOUT COVER		Iott M, Neben-Wittich M, Quevedo JF, Miller RC. Adjuvant chemoradiotherapy for resected pancreas cancer. *World J Gastrointest Surg* 2010; 2(11): 373-380 http://www.wjgnet.com/1948-9366/full/v2/i11/373.htm
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NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

LAUNCH DATE
November 30, 2009

SPONSOR
Beijing Baishideng BioMed Scientific Co., Ltd.,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
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Fax: 0086-10-8538-1893
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PUBLISHING
Baishideng Publishing Group Co., Limited,
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai,
Hong Kong, China
Telephone: 00852-5804-2046
E-mail: baishideng@wjgnet.com
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Room 903, Building D, Ocean International Center,
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Telephone: 0086-10-8538-1892
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http://www.wjgnet.com

ONLINE SUBSCRIPTION
One-Year Price 216.00 USD

PUBLICATION DATE
November 27, 2010

CSSN
ISSN 1948-9366 (online)

EDITORIAL OFFICE
Jin-Lei Wang, Director
World Journal of Gastrointestinal Surgery
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
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WJGS World Journal of Gastrointestinal Surgery

A peer-reviewed, online, open-access journal of gastrointestinal surgery

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World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v2.i11.373

World J Gastrointest Surg 2010 November 27; 2(11): 373-380
ISSN 1948-9366 (online)

EDITORIAL

Adjuvant chemoradiotherapy for resected pancreas cancer

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Received: May 29, 2010 Revised: September 5, 2010
Accepted: September 12, 2010
Published online: November 27, 2010

Abstract

The purpose of this article is to review pertinent literature assessing the evidence regarding adjuvant chemoradiotherapy for adenocarcinoma of the pancreas following curative resection. This review looks at randomized controlled studies with the emphasis on adjuvant chemoradiotherapy. In assessing the evidence from the studies reviewed in this article, the trials have been grouped according to the positive or negative results for or against adjuvant treatment. In addition, data from two large, single-institution studies affirming the role for adjuvant chemoradiotherapy has been included. Understanding the evidence from all of the randomized studies is important in shaping current practice recommendations for adjuvant therapy of surgically resected pancreas cancer. Adjuvant chemoradiotherapy following surgery is the current approach at many cancer treatment centers in the United States. In Europe, chemotherapy alone is the preferred adjuvant therapy. However, the type of adjuvant treatment recommended remains controversial due to conflicting study results. The debate will likely continue. Current practice should be based on the weight of evidence available at this time, which is in favor of adjuvant chemotherapy with chemoradiotherapy.

Key words: Pancreas cancer; Radiotherapy; Chemotherapy; Adjuvant

Peer reviewers: Sunil Krishnan, MD, Professor, Department of Radiation Oncology, MD Anderson Cancer Center, Unit 097, 1515 Holcombe Blvd, Houston, TX 77030, United States; Masashi Ishikawa, MD, PhD, Professor, Department of Surgery, Tokushima Red Cross Hospital, 103 Irinokuchi, Komatsushima city, Tokushima, Masa 1192, Japan

Iott M, Neben-Wittich M, Quevedo JF, Miller RC. Adjuvant chemoradiotherapy for resected pancreas cancer. *World J Gastrointest Surg* 2010; 2(11): 373-380 Available from: URL: http://www.wjgnet.com/1948-9366/full/v2/i11/373.htm DOI: http://dx.doi.org/10.4240/wjgs.v2.i11.373

INTRODUCTION

The most recent cancer statistics show that even though pancreatic cancer accounts for only 3% of all cancer cases, it remains the fourth most prevalent cause of cancer death among men and women (6% of cancer deaths for both sexes) in the United States. The outlook continues to be bleak considering that only 5% of patients diagnosed with pancreatic cancer will survive to 5 years. This survival rate has persisted, essentially unchanged, over the past few decades. The American Cancer Society's most recent projected estimates indicate there will be 42 470 new pancreas cancer diagnoses per year and 35 420 subsequent deaths. Surgery continues to be vitally important in achieving a potential cure for these patients. However, only a minority of pancreatic cancer patients have resectable disease at the time of diagnosis[1,2].

To date, surgery has been considered the mainstay for optimal treatment of pancreatic cancer and this situation is likely to continue for the foreseeable future. Unfortu-

nately, due to the aggressive nature of this cancer, even surgical resections with histologically negative margins (R0) do not affect a cure for the majority of patients. Therefore, adjuvant therapy must be considered for improvement in survival rates of patients who have undergone a potentially curative resection.

LITERATURE REVIEW

Prospective, randomized trials are the gold standard in evaluating treatment outcomes for adjuvant treatment of pancreatic cancer. However, randomized studies evaluating adjuvant chemoradiotherapy following curative resection for pancreatic cancer have produced inconsistent results. The conflicting findings from these studies make it difficult for clinicians to recommend optimal effective adjuvant treatment. Current recommendations by the National Comprehensive Cancer Network are for adjuvant therapy (chemotherapy and/or chemoradiotherapy) after surgery[3]. Therefore, the objective of this article is to assess and clarify current evidence and the underlying principles for recommending adjuvant chemoradiotherapy for patients with a resected pancreatic cancer.

Evidence for adjuvant chemoradiotherapy in randomized trials

Gastrointestinal Tumor Study Group 9173 trial: The first prospective, randomized, multi-institutional study for determining the effectiveness of adjuvant chemoradiotherapy for pancreas cancer was conducted by Kalser and Ellenberg[4]. In this seminal trial, 43 patients with histologically confirmed non-metastatic pancreatic adenocarcinoma with R0 surgical resections were randomly assigned to observation (22) or chemoradiotherapy (21). Radiotherapy was given in two 20 Gy courses separated by a two-week break. Concomitant, bolus 5-fluorouracil (5-FU) chemotherapy was administered on the first 3 d of each two-week course of radiotherapy. The study protocol also called for weekly maintenance 5-FU chemotherapy following completion of adjuvant chemoradiotherapy or until evidence of disease recurrence.

This study demonstrated a statistically significant prolonged survival rate for patients who received adjuvant chemoradiotherapy following surgery. A 20-mo median survival was achieved with adjuvant chemoradiotherapy as compared to 11 mo for patients who had surgery alone. A nonrandomized, confirmatory study with 30 additional patients given adjuvant chemoradiotherapy as dictated by the study protocol [conducted by Gastrointestinal Tumor Study Group (GITSG)] provided additional evidence substantiating the results of the randomized trial.

The size and extent of tumor at surgery and the Eastern Cooperative Oncology Group performance status were strongly predictive of overall survival. The most obvious limitation of this study was the small number of patients studied. Other adverse aspects of the study included the prolonged 8-year accrual time of study participants, the lack of a central standardized quality assurance for radiotherapy, the delay in starting adjuvant treatment after surgery (protocol time limit was 4-10 wk), and the small number of patients (2) who received the protocol prescribed maintenance chemotherapy following adjuvant chemoradiotherapy[4,5]. The findings from GITSG provided the incentive for performing additional larger studies such as the trial conducted by the European Organisation for Research and Treatment of Cancer (EORTC).

European Organisation for Research and Treatment of Cancer: This study was the second randomized, multicenter trial performed to look at the value of adjuvant chemoradiotherapy following surgery. Twenty-nine institutions across Europe participated in this trial. This was an attempt to validate results noted in the GITSG randomized study. The treatment protocol was similar to the GITSG trial in that radiotherapy was given in two, 20 Gy courses separated by a two-week break using a 3-4 field technique. However, chemotherapy differed from the GITSG study because concomitant chemotherapy was not given in bolus doses; it was administered via continuous infusion during the first two-week course of radiotherapy and then for either 0, 3 and 5 d during the second course of radiotherapy as determined by prior toxicity/patient tolerance during the first course. Another variance from the previous study was that there was no maintenance chemotherapy given following adjuvant chemoradiotherapy. Participants in this study (as determined by central pathology review) had either a resected T1-2N0-1aM0 adenocarcinoma of the head of the pancreas (114) or T1-3N0-1aM0 periampullary adenocarcinoma (104). The trial required patients to start adjuvant treatment within two to eight weeks of surgery. Following surgery, patients were randomized to observation (108) and treatment (110). Following removal of ineligible patients (five patients in the observation arm and six patients in the treatment arm), there were 103 patients observed and 104 patients treated.

The reported findings indicated that adjuvant chemoradiotherapy did not demonstrate an advantage for disease progression-free survival or overall survival. The observation group and treatment group had a progression-free survival of 16 and 17.4 mo respectively. Median overall survival for the observation and treatment groups were 19 and 24.5 mo respectively, and 2-year survival rates of 41% and 51% in the respective groups ($P = 0.208$). When evaluating only head of pancreas cancer patients, the authors noted a greater divergence between the groups with a median survival of 12.6 mo in the observation group and 17.1 mo in the treatment group. Although there was a trend for improvement with adjuvant chemoradiotherapy, it did not reach statistical significance ($P = 0.099$) using a two-sided log-rank test[6].

The inclusion of patients with positive surgical margins (R1) and patients with periampullary cancer complicated the interpretation of the trial results. Periampullary cancer is known to have a better prognosis over pancreatic cancer. Other limitations of this study include the lack of a centralized quality assurance for radiotherapy and the absence of maintenance chemotherapy following chemoradiotherapy.

Critics have since argued that a more appropriate statistical test to assess for improvement or harm (implied by the GITSG trial) would be to use a one-sided log-rank test as opposed to a two-sided log-rank test. Reanalysis of the data using the one-sided log-rank test suggests a statistically significant improvement in overall survival at two years for pancreatic cancer patients (P = 0.049). On this basis, the findings from this trial would be considered a positive trial for adjuvant chemoradiotherapy[7,8]. Similar benefits of improved survival have been noted in more recent randomized-controlled cooperative trials directed by the Radiation Therapy Oncology Group (RTOG) 97-04 study and the Charité Onkologie Phase Ⅲ trial.

RTOG 97-04 study: Regine *et al*[9] conducted the most contemporary, multi-institutional, randomized trial assessing the effectiveness of adding gemcitabine chemotherapy to adjuvant 5-FU-based chemoradiotherapy. This study was not intended to confirm the utility of adjuvant chemoradiotherapy with 5-FU since it was included in both regimens. This intergroup trial (from July 1998 through July 2002) evaluated resected pancreatic cancer patients and stratified them according to pathologic stage T1-4N0-1M0 and margin status (positive, negative or unknown). There were two treatment arms to which patients were randomized. One regimen called for 5-FU chemotherapy given via continuous venous infusion (CVI) for three weeks followed by chemoradiotherapy (using 5-FU). Then 3 to 5 wk later, this was followed by additional (CVI) 5-FU chemotherapy for 4 wk, 2 wk off and then repeated for another 4 wk. The second regimen involved once weekly gemcitabine chemotherapy for 3 wk followed by chemoradiotherapy (using 5-FU). Then 3 to 5 wk later, this was followed by further weekly gemcitabine chemotherapy for 3 wk then 1 wk off, repeated for a total of 3 cycles. There was no observation arm since RTOG considers chemoradiotherapy the current standard of care for resected pancreatic cancer. Radiotherapy (after central review) was given over a period of 5.5 wk (unlike GITSG and EORTC trials which had a split-course) to a dose of 50.4 Gy at 1.8 Gy/fraction per day along with concurrent continuous infusion 5-FU chemotherapy.

Of the 538 patients enrolled, 451 were eligible for the study. The analysis of patients with adenocarcinoma of the head of the pancreas (388) demonstrated that patients receiving the gemcitabine-based regimen had a 20.5-mo median survival and a 31% 3-year survival as opposed to the 5-FU-based regimen with 16.9 mo and 22% respectively, although this did not reach statistical significance (P = 0.09). On univariate analysis, the addition of gemcitabine to adjuvant, 5-FU based chemoradiotherapy was associated with a trend toward survival benefit but without a statistically significant improvement in overall or disease-free survival. However, with adjustments made for prognostic variables, multivariate analysis of head of pancreas tumors revealed that the treatment effect of the gemcitabine-regimen yielded a statistically significant effect for enhanced survival (P = 0.05 with a 0.80 hazard ratio). The study authors asserted that accounting for the prognostic variables with multivariate analysis is a more accurate assessment of treatment outcome. Therefore, this study was included as evidence for adjuvant chemoradiotherapy. However, the primary endpoint of this trial to detect a statistically significant improvement in overall and disease-free survival for resected pancreatic cancer patients receiving adjuvant therapy with the addition of gemcitabine to chemoradiotherapy was not achieved. The trial only demonstrated that a trend toward improved survival. Confounding the results of this study is the fact, that many patients were given salvage chemotherapy at the time of disease recurrence with a majority of those receiving gemcitabine for salvage treatment. This salvage therapy probably lessened the capacity to discover a significant survival benefit[7,9,10].

An important finding from this study is that lymph node involvement was found to be a poor prognostic factor, demonstrating statistical significance with a P-value of 0.001. Tumor size (< 3 cm or ⩾ 3cm) and surgical margin status (negative, positive or unknown) did not reach statistical significance as prognostic factors. Further analysis of postoperative CA 19-9 levels as a secondary endpoint of the study revealed that a postresection CA 19-9 value of ⩽ 90 U/mL was also an independent predictor for survival. A significant increased risk of death was associated with CA 19-9 levels > 90 (P < 0.001)[7,9-12]. The study authors recommended the inclusion of gemcitabine-based therapy in future trials of adjuvant chemoradiotherapy. Even without the use of radiotherapy, the evidence for the positive effect of gemcitabine-based chemotherapy has been seen, as noted in a study performed by the German Charité Onkologie group.

Charité Onkologie Phase Ⅲ trial: This collaborative German and Austrian, multi-institutional, randomized, controlled trial (July 1998 to December 2004) conducted by Oettle *et al*[13] sought to determine if resected pancreatic cancer patients would see a benefit in disease-free survival of six months or greater when given gemcitabine-based adjuvant chemotherapy. A total of 368 patients recruited were randomized to receive gemcitabine (n = 186) or observation (n = 182) following a macroscopic complete R0 or R1 resection. Presurgical staging required patients to have a T1-T4N0-N1M0 disease. Patients were stratified according to T-stage (T1-2 *vs* T3-4) and lymph node status (positive or negative). Of these participants, seven were excluded from each arm due to enrollment criteria violations. In the end, 179 patients received gemcitabine-based adjuvant chemotherapy and 175 patients were observed.

Chemotherapy for the gemcitabine group consisted of 6 cycles of gemcitabine (one weekly dose × 3 wk and one week off). Commencement of chemotherapy between postoperative day 10 and day 42 depending on wound status was recommended. There were 111 (62%) of patients received the complete 6 cycles of gemcitabine

and 90% received a minimum of one dose. At least 87% were given one complete cycle of adjuvant gemcitabine chemotherapy.

Findings from this cooperative study demonstrated an improvement in the median disease-free survival that was statistically significant. The median disease-free survival for participants receiving adjuvant gemcitabine chemotherapy was 13.4 mo along with an estimated 3-year and 5-year disease-free survival of 23.5% and 16.5% as compared to 6.9 mo and 7.5% and 5.5% for the observation group ($P < 0.001$). However, overall survival only showed a trend toward improvement; it did not reach statistical significance. Follow up performed over a median of 53-mo demonstrated that participants receiving gemcitabine had a 22.1 mo median survival as compared to participants in the observation group with a 20.2 mo median survival ($P = 0.06$).

A limitation of this study was the lack of central review for validation of surgical resection and staging. In addition, participants in the observation group were given gemcitabine and other chemotherapy upon relapse of disease. This limits the study's capacity to identify a benefit in overall survival. Although the change in overall survival did not show statistical significance, this trial does demonstrate that adjuvant gemcitabine chemotherapy has a positive affect on disease-free survival. This trial's results combined with the results of RTOG 97-04 (chemoradiotherapy) adds weight to the evidence in favor of adjuvant therapy for resected pancreatic cancer[9,11,13]. However, there are other studies with negative results that should be considered when evaluating recommendations for adjuvant chemoradiotherapy.

Evidence against adjuvant chemoradiotherapy in randomized trials

European Study Group for Pancreatic Cancer trial: In this complex, multicenter, prospective, randomized study (February 1994 to June 2000), Neoptolemos *et al*[14] attempted to answer questions regarding the utility of adjuvant chemotherapy and adjuvant chemoradiotherapy *vs* no adjuvant therapy for potentially curatively resected pancreatic cancer patients. The updated analysis of the original study was done by way of comparison using a (2 × 2) factorial design with participants randomized to groups defined as (1) observation (no adjuvant therapy); (2) adjuvant chemoradiotherapy; (3) adjuvant chemotherapy; and (4) chemotherapy following adjuvant chemoradiotherapy. This design was used to detect the independent effect of each treatment and its interaction with other treatments in the study.

The regimen for chemoradiotherapy involved a similar course of radiotherapy as the GITSG trial which was given as two, 20 Gy courses separated by a two-week break. As well, the 5-FU chemotherapy was administered in bolus doses on the first three days of each two-week course of radiotherapy. The adjuvant chemotherapy regimen included a bolus dose of leucovorin followed by bolus 5-FU on five consecutive days of a 28-d cycle for a total of six cycles. The combined regimen (chemoradiotherapy + chemotherapy) involved the chemoradiotherapy regimen noted above followed by the previously described 28-d cycle chemotherapy regimen.

As patients ($n = 289$) were randomized within the 2 × 2 factorial design, the group breakdown was as follows: Observation (no adjuvant therapy) group ($n = 69$); chemoradiotherapy group ($n = 73$); chemotherapy group ($n = 75$) and chemoradiotherapy with additional chemotherapy group ($n = 72$). As the authors assessed group outcomes, the factorial design then allowed for combination of the randomized patient groups noted above into subsets as follows; patients assigned to receive chemoradiotherapy [chemoradiotherapy (73) + chemoradiotherapy and chemotherapy (72) = 145] *vs* assigned not to receive chemoradiotherapy [chemotherapy (75) + observation (69) = 144] and the patients assigned to chemotherapy [chemotherapy (75) + chemoradiotherapy and chemotherapy (72) = 147] *vs* assigned not to receive chemotherapy alone [observation (69) + chemoradiotherapy (73) = 142].

Interpretation of the results from this trial is complicated due to its complex structure. There was a median follow up of 47 mo. Assessment of a 2-year survival rate was its primary endpoint. Calculation of survival rate was determined by the date of surgery until death from disease or other cause. Measurement of secondary endpoints involved the prevalence of adverse treatment effects, recurrence of disease and quality of life.

Patients assigned to the chemoradiotherapy subset ($n = 145$) had a median survival of 15.9 mo as compared to a median survival of 17.9 mo for patients assigned not to receive chemoradiotherapy subset ($n = 144$) with a *P*-value of 0.05. The 2-year and 5-year survival estimates were 29% and 10% for the chemoradiotherapy subset (145) and 40% and 20% respectively in the no chemoradiotherapy subset (144). In the chemotherapy subset ($n = 147$), the median survival was 20.1 mo as compared to 15.5 mo in the patients who did not receive chemotherapy subset ($n = 142$) with a *P*-value of 0.009. The 2-year and 5-year survival estimates were 40% and 21% for the chemotherapy subset (147) and 30% and 8% in the no chemotherapy subset (142). Additional analyses of survival demonstrated that the observation (no adjuvant therapy) group (69) had a 16.9 mo median survival and a 5-year survival estimate of 11% as compared to a 13.9 mo median survival and a 7% 5-year survival estimate of the chemoradiotherapy group (73). A median survival of 21.6 mo and estimated 5-year survival rate of 29% was seen for patients receiving chemotherapy (75) as compared to 19.9 mo and a 13% 5-year survival estimate for the combination treatment (chemoradiotherapy + chemotherapy) group (72). Other outcome analysis found that increased tumor differentiation, tumor size > 2 cm and positive lymph nodes had a significant adverse affect on survival. There was no statistically significant difference in quality of life measures between the groups[14].

This trial was the largest randomized study to date attempting to examine the advantage of adjuvant treatment (chemoradiotherapy and maintenance chemotherapy) for resected pancreatic cancer. The positive aspect of this

study was that a survival advantage was noted for resected pancreatic cancer patients who received adjuvant chemotherapy. However, this study is considered negative for chemoradiotherapy as it was found to adversely affect survival and even more so than no adjuvant therapy. Critics have raised concern that there were notable delays in treatment start time with a mean of 61 d for the chemoradiotherapy group as opposed to 48 d for the chemotherapy group. There is also concern about selection bias and whether the group of patients undergoing chemoradiotherapy had a poorer performance status than patients in the no adjuvant therapy group which had a better survival outcome. The question was raised whether or not toxicity from the first treatment in the consecutive treatment group (chemoradiotherapy followed by chemotherapy) affected compliance with the second portion of therapy. A limitation of this study was that there was no central standardized quality assurance for radiotherapy. Critics also note that the split-course of radiotherapy used in this trial is now considered outdated. Further confounding the findings of European Study Group for Pancreatic Cancer Trial, is the fact that physicians enrolling patients to the trial were also allowed to give other "background" chemotherapy or chemoradiotherapy, thus making interpretation of the trial results difficult[7,15-17]. The results of this trial in addition to the initial analysis of the EORTC trial effectively changed the practice in Europe. Chemotherapy alone is currently the preferred treatment for resected pancreatic cancer patients. However, in many centers in the United States, the recommendation for adjuvant therapy continues to be a combination of postoperative chemotherapy and chemoradiotherapy. Therefore, review of two large, single-institution studies of adjuvantly treated resected pancreatic cancer patients are included here. These studies reflect the general practice for adjuvant treatment usually given to resected pancreatic cancer patients in the United States.

Evidence for adjuvant therapy in large single-institution studies

The Johns Hopkins Hospital experience: A large study of prospectively collected data of resected pancreatic cancer patients (n = 616) at Johns Hopkins Hospital was conducted by Herman *et al*[18]. The study patients underwent a pancreaticoduodenectomy followed by adjuvant chemoradiotherapy or observation (from August 30, 1993 through February 28, 2005). Patients with T4 or M1 disease were excluded from analysis. Findings from this study demonstrated a significant improvement in overall survival for patients that underwent adjuvant chemoradiotherapy following a pancreaticoduodenectomy compared with those patients who had surgery alone. There was a 21.2 mo median survival for adjuvantly treated patients as compared to 14.4 mo for surgery-only patients ($P < 0.001$). The 2-year and 5-year survival rates for resected patients were 43.9% and 20.1% following adjuvant treatment as compared to 31.9% and 15.4% respectively without adjuvant chemoradiotherapy. The study authors also noted that adjuvant chemoradiotherapy provided a survival benefit even when high risk tumor features (high histologic grade, nodal involvement and positive surgical margins) were present.

The Mayo Clinic experience: A similar retrospective study was conducted by Corsini *et al*[19] at Mayo Clinic for stage Ⅰ-Ⅱ, T1-3N0-1M0 pancreas cancer patients (n = 454) who had undergone a R0 resection and postoperative adjuvant chemoradiotherapy (1975 to 2005). The retrospective analysis demonstrated that providing adjuvant chemoradiotherapy after surgery significantly improved overall survival. There was a 25.2 mo *vs* a 19.2 mo median survival for patients receiving adjuvant treatment (n = 274) *vs* no adjuvant treatment (n = 180) following surgery (P = 0.001). The authors noted a 2-year and 5-year survival of 50% and 28% for the adjuvant therapy group as opposed to 39% 2-year and 17% 5-year survival for surgery-alone group. They also found that positive lymph nodes and tumors with high histological grade adversely affected prognosis. In addition, they noted that patients receiving adjuvant treatment had a higher number of these adverse prognostic factors.

The Johns Hopkins Hospital & Mayo Clinic Collaborative study: Hsu *et al*[20] took a collaborative approach by combining the single-institution data noted above from Johns Hopkins Hospital and Mayo Clinic in order to assess predictive factors for survival following surgery, and to determine the benefit of adjuvant chemoradiotherapy stratified by risk groups. They also performed propensity score analysis as well as matched-pair analysis to correct for treatment selection bias associated with retrospective data. There were 1092 patients who underwent resection who were appropriate for review. The adjuvant chemoradiotherapy group (n = 583) and surgery-alone group (n = 509) survival did not vary significantly by institution. Patients who received adjuvant therapy were younger (median age 64.7 years) than the no adjuvant therapy group (median age 70.2 years) with a P-value < 0.001. The adjuvant therapy group had higher grade (3 or 4) tumors (59%) and greater positive surgical margins (35%) as compared to 51% and 31% respectively for the surgery alone group. However, adjuvant chemoradiotherapy after surgery was found to significantly improve survival in spite of the age of patient, and the status of the tumor, surgical margin or lymph nodes. Following propensity score analysis, overall survival improved by about 33% following adjuvant chemoradiotherapy ($P < 0.001$). Median survival, 2-year and 5-year survival were better with 21.1 mo, 44.7% and 22.3% as compared to 15.5 mo, 34.6% and 16.1% for those not receiving adjuvant therapy ($P < 0.001$).

Analysis of these large single-institution treatment data affirms the results of the randomized studies showing positive results. Adjuvant chemoradiotherapy for patients with a resected pancreatic cancer provides a survival benefit. Adjuvant therapy with chemotherapy alone or with chemoradiotherapy should remain an essential part of the treatment recommendations for resected pancreatic cancer.

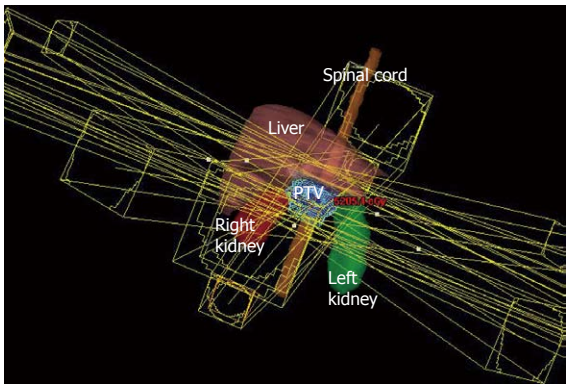

Figure 1 External beam radiotherapy beam portal arrangement showing a six field approach to irradiating the post-operative bed and regional lymphatic region planning target volume at risk. PTV: Planning target volume.

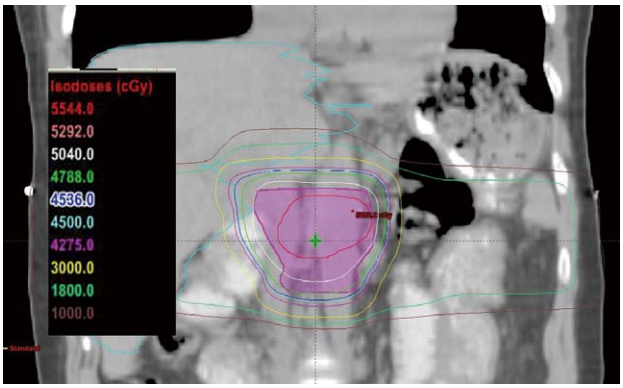

Figure 2 Coronal isodose plot showing typical isodose distribution in the retroperitoneal region illustrating sparing of the liver from high radiation dose.

RECOMMENDATIONS

Our current approach for adjuvant therapy for pancreas cancer includes a complete restaging following their resection. For patients with non-metastatic disease, a discussion is carried out regarding the potential benefits and side effects of either chemotherapy alone *vs* chemotherapy followed by chemoradiotherapy and then further chemotherapy. For patients with higher risk factors for local-regional recurrence such as local extension beyond the pancreas, an incomplete resection (R1/R2 resection), or positive lymph nodes, chemoradiotherapy may be considered following initial treatment with chemotherapy, similar to that of the RTOG 97-04 trial. Our previous analysis of patients undergoing resection at the Mayo Clinic for pancreas cancer showed that the risk of recurrence and death from tumor progression rises significantly for patients with these risk factors. Survival is proportionally greater following adjuvant therapy in cases with higher numbers of risk factors despite the overall higher risk of recurrence[21].

Patients receive two months of gemcitabine, followed by a second restaging procedure consisting of a repeat computed tomography scan of the abdomen and pelvis, chest X-ray, and laboratory studies including a CA 19-9 analysis. If patients have no evidence of metastatic progression, they then go on to receive 50.4 Gy of external beam radiotherapy in 1.8 per day fractions along with either radiosensitizing 5-FU chemotherapy given by continuous intravenous infusion or capecitabine. Following completion of this six week course of therapy, patients have a 3 to 4 wk recovery period before moving on to a further two months of gemcitabine chemotherapy. Radiotherapy is directed at the bed of resection, areas adjacent to the original tumor at risk for occult, direct local spread in the retroperitoneum and along vascular structures, and lymph node regions at risk. Details of this technique have been published elsewhere by Corsini *et al*[19].

However, techniques for radiotherapy treatment delivery have changed over time. Currently, we favor a non-coplanar, six field approach for radiotherapy delivery that allows for enhanced sparing of normal tissues such as the liver, kidneys, and spinal cord. Anterior and posterior radiotherapy beams are angled inferiorly and superiorly to reduce the dose to the liver and kidneys, while the remaining radiotherapy dose is delivered through opposed lateral beams and two anterior oblique beams angled 45 degrees to either side of vertical. Figures 1-3 illustrate a typical treatment geometry and isodose curves in the axial and coronal planes for a case receiving postoperative radiotherapy for resected pancreas cancer.

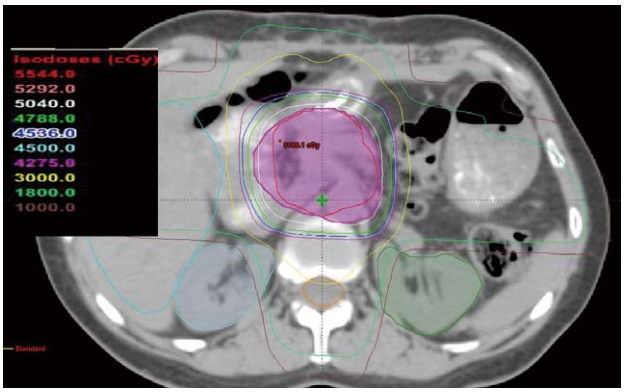

Figure 3 Axial isodose plot showing typical isodose distribution in the retroperitoneal region illustrating sparing of the kidneys from high radiation dose.

CONCLUSION

At this time, surgical resection will continue to be the most important first step in the treatment of pancreas cancer. The review of eminent, randomized-controlled studies (Table 1) is important in understanding the current practice for recommendations for adjuvant therapy of surgically resected pancreas cancer. The examination of the two single-institution studies completed by Johns Hopkins Hospital and Mayo Clinic (Table 1) adds weight to the evidence in favor of both adjuvant chemotherapy and chemoradiotherapy. The positive randomized-controlled trials and the large, single-institution studies reflect the current approach offered at many cancer treatment centers in the United States. However, the type of

Table 1 Trial comparison

Trial/authors, yr	Adjuvant therapy	Patients (*n*)	Median survival (mo)	Median disease free survival (mo)	Estimated 5-yr survival (%)	*P*-value
Evidence for adjuvant chemoradiotherapy in randomized trials						
GITSG 9173/	Chemoradiotherapy (5-FU)	21	20	11	18	0.035
Kalser *et al*[4], 1985	No adjuvant therapy	22	11	9	0	
EORTC Phase Ⅲ/	Chemoradiotherapy (5-FU)	104	24.5[a] 17.1[b]	17.4[a]	28[a]	0.099[a]
Klinkenbijl *et al*[6], 1999	No adjuvant therapy	103	19[a] 12.6[b]	16[a]	22[a]	0.049[c]
RTOG 97-04/	Chemoradiotherapy (5-FU)	230	16.9		22[d]	0.09
Regine *et al*[9], 2008	Chemoradiotherapy (gemcitabine)	221	20.5		31[d]	
CONKO Phase Ⅲ/	Chemotherapy (gemcitabine)	186	22.1	13.4	18	< 0.001[e]
Oettle *et al*[13], 2007	No adjuvant therapy	182	20.2	6.9	0	0.06[f]
Evidence against adjuvant chemoradiotherapy in randomized trials						
ESPAC-1/	Chemotherapy (CT) (5-FU)	75	21.6		29	0.05 [(CT/RT), (CT/RT + CT) *vs* (CT), (no CT/RT)]
Neoptolemos *et al*[14], 2004	Chemoradiotherapy (CT/RT) (5-FU)	73	19.9		13	
	Chemoradiotherapy + chemotherapy (CT/RT + CT) (5-FU)	72	13.9		7	0.009 [(CT), (CT/RT + CT) *vs* (CT/RT), no (CT/RT)]
	No adjuvant therapy	69	16.9		11	
Evidence for adjuvant therapy in large single-institution studies						
Johns Hopkins Hospital experience/	Chemoradiotherapy (5-FU)	271	21.2		20.1	< 0.001
Herman *et al*[18], 2008	No adjuvant therapy	345	14.4		15.4	
The Mayo Clinic experience/	Chemoradiotherapy (5-FU)	274	25.2		28	0.001
Corsini *et al*[19], 2008	No adjuvant therapy	180	19.2		17	
The Johns Hopkins Hospital & Mayo Clinic Collaborative study/	Chemoradiotherapy (5-FU)	583	21.1		22.3	< 0.001
Hsu *et al*[20], 2010	No adjuvant therapy	509	15.5		16.1	

[a]Based on the two-sided log-rank test; [b]Results for patients with pancreatic cancer only, differences not significant; [c]Based on the reanalysis using the one-sided log-rank test; [d]Three years survival; [e]Median disease-free survival; [f]Overall survival. GITSG: Gastrointestinal Tumor Study Group; 5-FU: 5-fluorouracil; EORTC: European Organisation for Research and Treatment of Cancer; RTOG: Radiation Therapy Oncology Group; CONKO: Charité Onkologie; ESPAC-1: European Study Group for Pancreatic Cancer Trial; CT: Chemotherapy; RT: Radiation therapy.

adjuvant treatment recommended remains controversial. In Europe, chemotherapy alone (5-FU/leucovorin or gemcitabine) is the preferred adjuvant therapy. The controversy regarding adjuvant therapy is likely to continue. However, this should not deter the search for the optimal treatment of this deadly disease. Current practice recommendations should be based on the weight of evidence in favor of adjuvant chemotherapy with chemoradiotherapy.

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S- Editor Wang JL **L- Editor** Hughes D **E- Editor** Lin YP

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v2.i11.381

World J Gastrointest Surg 2010 November 27; 2(11): 381-384
ISSN 1948-9366 (online)

REVIEW

An ongoing dispute in the management of severe pancreatic fistula: Pancreatospleenectomy or not?

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Received: June 1, 2010 Revised: September 18, 2010
Accepted: September 26, 2010
Published online: November 27, 2010

Abstract

The aim of this manuscript is to review controversies in managing severe pancreatic fistula after pancreatic surgery. Significant progress in surgical technique and perioperative care has reduced the mortality rate of pancreatic surgery. However, leakage of the pancreatic stump still accounts for the majority of surgical complications after pancreatic resection. Various strategies have been employed in order to manage pancreatic fistula. Nonetheless high grade pancreatic fistula evokes controversy in relation to the choice of treatment. A Medline search was performed, with regard to conservative treatment options versus completion pancreatectomy for the management of pancreatic fistula grade C. Pancreatic fistula rates remain unchanged with an incidence ranging from 5%-20% and this is considered as the most important cause of postoperative death. Many authors claim that completion pancreatectomy has probably lost its role in favour of interventional radiology procedures, while others believe that completion pancreatectomy continues to have a place in the management of patients with severe clinical deterioration after pancreatic fistula who do not respond to non-surgical interventions. There is no agreement on the best clinical management of severe pancreatic fistula after pancreatic surgery. Completion pancreatectomy is reserved for patients not improving with conventional measures.

Key words: Pancreatic fistula; Pancreatoduodenectomy; Pancreatospleenectomy; Completion pancreatectomy; Percutaneous drainage

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Dellaportas D, Tympa A, Nastos C, Psychogiou V, Karakatsanis A, Polydorou A, Fragulidis G, Vassiliou I, Smyrniotis V. An ongoing dispute in the management of severe pancreatic fistula: Pancreatospleenectomy or not? *World J Gastrointest Surg* 2010; 2(11): 381-384 Available from: URL: http://www.wjgnet.com/1948-9366/full/v2/i11/381.htm DOI: http://dx.doi.org/10.4240/wjgs.v2.i11.381

INTRODUCTION

Pancreatic surgery has improved dramatically during the past two decades. Mortality rates after Whipple's procedure in the 1980s exceeded 20%, but nowadays mortality has been reduced to less than 5% in high volume centers[1]. At present the single most important cause of morbitity and mortality after pancreatoduodenectomy (PD) is

pancreatic leakage and fistula (PF)[2]. Some authors have named pancreatic anastomosis the "Achilles heel" of pancreatic surgery because it has the highest rate of surgical complications among all abdominal anastomoses[3]. Also PF can lead to prolonged hospital stay and increase the cost of treatment. Various strategies have been employed in order to prevent and manage PF, but when severe grade PF occurs controversy exists about the treatment of choice. Many authors insist that completion pancreatectomy (CP) continues to have a place in patients with severe septicemia and clinical deterioration, while others suggest that CP has lost its role and conservative management is the treatment of choice even for grade C PF. The aim of this study is to highlight the most effective strategy in the management of grade C PF.

DEFINITIONS

There are many different definitions of pancreatic fistula in the literature, based on a multitude of parameters and this renders comparison between studies difficult. A valuable clinical definition was published in 2005 by Bassi *et al*[1] and the International Study Group for postoperative Pancreatic Fistula. A pancreatic fistula represents a failure in healing of the pancreato-enteric anastomosis or a parenchymal leak not directly related to an anastomosis. Three different grades of PF (grades A, B, C) are defined according to the clinical impact on the patient's clinical course (Table 1). In terms of measures, PF is a drain output of any measurable volume of fluid on or after postoperative day 3, with an amylase content greater than 3 times the serum amylase activity.

Grade A PF is the most common grade and has no major clinical impact. It is managed with gradual removal of the drains that were placed intraoperatively.

Grade B PF is a clinically relevant fistula and it may be associated with abdominal pain, fever, leukocytosis. In most cases the patient is supported with total parenteral nutrition (TPN) or enteral nutrition. The drains should be left in place and if there is any evidence of abdominal collections on CT scan or US, further drainage is required. Also, antibiotics and somatostatin analogues are sometimes employed.

Grade C PF is the most severe, with a high mortality rate. When grade C PF occurs it usually presents with abscesses, peritonitis, sepsis and hemorrhage. These patients require major interventions. Treatment of this life-threatening condition can be conventional, with image-guided or operative drainage, or more aggressive with completion pancreato-spleenectomy.

MANAGEMENT OF PANCREATIC FISTULA GRADE C IN SEVERAL STUDIES

Pancreatic fistula incidence varies among different centers between 2%-30% depending also upon the definition used[2-4] (Table 2).

Cullen *et al*[5] studied 375 patients who underwent PD for a variety of indications. They reported that 66 patients (18%) had pancreatic leakage, of whom only 18 (27%) could be graded as grade C. Completion pancreatectomy was performed in 7 patients with a high degree of destruction and inflammation in the retroperitoneum. The authors concluded that although CP had a very high mortality rate in the treatment of a dehisced pancreato-jejunal anastomosis, it may be the only option available to salvage the patient, and lesser procedures could have proved ineffective in controlling the leak.

High rates of mortality and morbidity after CP have also been reported by Farley *et al*[6] (24% and 41% respectively). Their study was conducted on 458 patients who underwent CP after various severe complications following Whipple's procedures, including PF. The authors concluded that re-evalaution and a decision to use CP is crucial and can be life-saving, when conventional measures have failed, and it should be performed early in the course of clinical deterioration of the patient. Another interesting study was published by van Berge Henegouwen *et al*[7] comparing drainage versus CP after pancreatic leakage. The authors claim that among 269 patients undergoing PD, 29 (11%) developed severe and persistent leakage of the anastomosis. They suggested that early CP is the treatment of choice, since they reported no mortality after this treatment option, in contrast with previous studies[5,6], while mortality was seen after managing PF with conventional measures. However, the grade of the PF in this study cannot be clearly defined as the definitions from Bassi were given after their study was published and it is possible that patients without severe deterioration were surgically managed without any resulting mortality.

In order to determine risk factors for PF grade C, Fuks *et al*[8] studied 680 patients who underwent PD in 5 digestive surgery departments in the northwest region of France. PF was defined according to the Bassi definition. The incidence of PF was 111 patients (16.3%) and PF grade C occurred in 36 patients (32 % of PF). The overall mortality rate due to PF grade C was 38.8%, The mortality rate for CP was one in two patients (50%). Mortality for operative drainage was reportedly 55%. No data were given for percutaneous drainage.

Table 1 Classification of pancreatic fistula (from Bassi *et al*[1])

	Grade A	Grade B	Grade C
Clinical conditions	Well	Often well	Ill, appearing bad
Specific treatment[1]	No	Yes/no	Yes
US/CT	Negative	Negative/positive	Positive
Persistent drainage after 3 wk[2]	No	No	Yes
Re-operation	No	No	Yes
Death related to PF	No	No	Possibly yes
Sings of infection	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/no	Yes/no

[1]Partial or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue, and/or minimal invasive drainage; [2]With or without a drain *in situ*. PF: Pancreatic fistula; US: Ultrasonography; CT: Computed tomography scan.

Table 2 Incidence and management of pancreatic fistula in different studies *n* (%)

Authors	*n*	Incidence of PF/ grade C PF	Treatment		Mortality rate	
			Conservative or surgical drainage	CP	Conservative	CP
Cullen *et al*[5], 1994	375	66 (18)/18 (4.8)	11 (61)	7 (39)	5 (8)	
Farley *et al*[6], 1996	458	NA	NA	17	NA	4 (24)
van Berge Henegouwen *et al*[7], 1997	269	29 (11)/NA	21	8	8 (38)	0
Fuks *et al*[8], 2009	680	111 (16.3)/36 (5.2)	34 (95)	2 (5)	14 (38.8)	
de Castro *et al*[9], 2005	459	41 (8.9)/27 (10.2)	18 (67)	9 (33)	6 (15)	0
Büchler *et al*[10], 2003	617	20 (3.2)/NA	NA	0	0	0
Haddad *et al*[11], 2009	117	35 (30)/14 (12)	9 (65)	5 (35)	2 (22)	3 (60)

PF: Pancreatic fistul; CP: Completion pancreatectomy; NA: Not available.

Additionally, de Castro *et al*[9] studied the optimal management of PF after PD. He used a different definition for PF. PF was defined as high amylase level in drain fluid (> 3 times serum level), or leakage proven by CT or US or re-laparotomy in combination with clinical deterioration of the patient. PF presented at 41 patients (8.9%) . Non-surgical drainage was performed in 14 of them. Drains placed intra-operatively were maintained in 7 of these patients and percutaneous drainage was conducted in the rest. The mortality rate was 15% (6 patients died). One of them underwent surgical drainage and three underwent surgical exploration and disconnection of the pancreatic-jejunal anastomosis, with preservation of a pancreatic remnant. No patient died of those who needed CP. Of the seven patients who survived after re-laparotomy and preservation of a pancreatic remnant, most were re-admitted suffering from necrosis, pseudocysts and fistulas. This strategy prevented diabetes mellitus, the major concern in the CP group, in approximately half of the patients although at the cost of an increased risk of postoperative death. This study concluded that CP continues to have a place in the management of patients with severe septicaemia after PF, who do not respond to non-surgical drainage procedures. However the PFs included in this study were not restricted to grade C as the Bassi definitions did not exist at the time of the study. Grade B fistulas were certainly included in the PFs that were managed in the study.

On the other hand, there are authors who do not support CP due to the mortality, morbidity and other consequences. Büchler *et al*[10] claimed that CP should no longer be considered in patients with a PF. They studied 617 patients who underwent pancreatectomy. The overall incidence of PF in this study was 3.2% (20 patients)with no mortality reported after PF. However no data are given concerning the severity of these PF cases. Seventeen of the 20 patients who developed this complication healed with conservative treatment, two underwent interventional drainage procedure after developing a low-output PF and a simultaneous peri-anastomotic abscess and only one required reoperation in order to deal with a high-output PF (> 200 mL/d). No patient underwent CP. The authors conclude that CP has probably lost its role in PF management. However, the data from this study cannot be compared with other studies as there is no correlation of the impact of PF with the patient overall status. As a result there is no way to exclude grade A and B PF cases which would have a better prognosis and would not require major interventions.

Haddad *et al*[11] published an article about the treatment of choice for PF after PD. In their study 121 patients underwent PD of which 35 (30%) developed PF. Of these 20 were managed conservatively and 14 were re-operated. Five underwent CP and overall mortality in the re-operated patients was 60% (3 patients). Nine patients underwent surgical debridement and drainage with 22% mortality (2 patients). This study suggests that CP should be performed only in patients with peritonitis and severe inflammation of the retroperitoneal space. Additionally, radiological or conservative surgical treatment of PF should be the preferred option, because extensive drainage and CP are procedures which have high mortality and morbidity rates. The authors also give emphasis on postoperative CP endocrine insufficiency and the associated morbidity.

MANAGEMENT CONTROVERSIES

Despite the extensive experience with pancreatic resection procedures and the decrease in overall complication rates and hospital stay, pancreatic leak rates remain unchanged[12]. Rates of postoperative mortality, wound infection, cardiac complications, intra-abdominal abscess, bile leak, hemorrhage from the rupture of a pseudo-aneurysm and frequency of re-operation are significantly greater in patients with PF. Consequently, prevention and effective management of these patients is a major concern for pancreatic surgeons[13]. Obviously the management of complications associated with PF requires a multidisciplinary approach involving the pancreatic surgeon, intensive care team and interventional radiologists[14]. PF grade A and B are well managed conservatively with TPN, somatostatin analogues, slow removal of the drains placed intra-operatively and percutaneous drainage of abdominal collections, if needed[4]. On the other hand PF grade C is a life-threatening condition and may require operative intervention when there is evidence of sepsis and/or organ dysfunction. The overall re-laparotomy rate has decreased, indicating that many complications can be managed by non-operative means. Once the operative approach is decided the degree of destruction and inflammation in the retro-peritoneum probably plays the major role in determining the operative

procedure for correcting the leaking pancreaticojejunal anastomosis. At the present time, the use of CP is under debate whereas conservative management is thought to be as a salvage solution equally efficient to CP. Although CP has high mortality rates, but lesser procedures may be ineffective in controlling the leak. This aggressive approach achieves sterilization of the infection source and has a decreased need for re-operation. However, it is a technically demanding procedure with major pitfalls as it leads, in most cases to splenectomy and, moreover, to endocrine insufficiency with potential lethal severe hypoglycaemia.

The preferred management strategy remains a matter of debate and generally depends on the severity of the leak and the surgeon's preference.

CONCLUSION

The operating skills of the surgeon and the clinical assessment of the patient are crucial in deciding on surgical intervention through completion pancreatectomy patients with PF grade C who do not clinically improve under conventional measures. Future studies should be designed according to strict and uniform criteria concerning the severity and degree of PF in order to evaluate the place of each therapeutic intervention for the management of this complication.

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S- Editor Wang JL **L- Editor** Hughes D **E- Editor** Lin YP

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v2.i11.385

World J Gastrointest Surg 2010 November 27; 2(11): 385-388
ISSN 1948-9366 (online)

CASE REPORT

Sporadic gastric carcinoid tumor successfully treated by two-stage laparoscopic surgery: A case report

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Received: June 15, 2010 Revised: September 20, 2010
Accepted: September 27, 2010
Published online: November 27, 2010

Key words: Gastric carcinoid; Laparoscopic surgery; Laparoscopy-assisted distal gastrectomy; Completion surgery; Submucosal tumor

Peer reviewer: Paolo Morgagni, MD, Departement of Surgical, GB Morgagni L Pierantoni General Hospital, Viale Forlanini 33, Forli 47100, Italy

Kinoshita T, Oshiro T, Urita T, Yoshida Y, Ooshiro M, Okazumi S, Katoh R, Sasai D, Hiruta N. Sporadic gastric carcinoid tumor successfully treated by two-stage laparoscopic surgery: A case report. *World J Gastrointest Surg* 2010; 2(11): 385-388 Available from: URL: http://www.wjgnet.com/1948-9366/full/v2/i11/385.htm DOI: http://dx.doi.org/10.4240/wjgs.v2.i11.385

Abstract

We report a case of sporadic gastric carcinoid tumor successfully treated by two-stage laparoscopic surgery. A 38-year old asymptomatic woman was referred to our hospital for evaluation of a submucosal tumor of the stomach. Endoscopic examination showed a solitary submucosal tumor without ulceration or central depression on the posterior wall of the antrum and biopsy specimens were not sufficient to determine the diagnosis. Endoscopic ultrasound revealed a tumor nearly 2 cm in diameter arising from the muscle layer and a computed tomography scan showed the tumor enhanced in the arterial phase. Laparoscopic wedge resection was performed for definitive diagnosis. Pathologically, the tumor was shown to be gastric carcinoid infiltrating the muscle layer which indicated the probability of lymph node metastasis. Serum gastrin levels were normal. As a radical treatment, laparoscopy-assisted distal gastrectomy with regional lymphadenectomy was performed 3 wk after the initial surgery. Finally, pathological examination revealed no lymph node metastasis.

INTRODUCTION

Gastric carcinoids are thought to be relatively rare tumors[1]. However, recently the prevalence of gastric carcinoids has risen, reported as 8.7% of all gastrointestinal carcinoid tumors in a large database[2]. In 1993, Rindi *et al*[3] advocated a classification of three subtypes of gastric carcinoid tumors, helpful for the prediction of malignant potential and commonly used. Among the three subtypes, type Ⅲ, sporadic carcinoid, is known to possess a more aggressive behavior pattern than other subtypes with a higher malignant potential. Therefore, the recommended treatment is aggressive surgical management in the same manner as gastric cancer[4-7].

In this report, we describe a case of sporadic gastric carcinoid tumor with the appearance of a submucosal tumor. It was successfully treated by two-stage less invasive surgery which involved laparoscopic wedge resection and laparoscopy-assisted distal gastrectomy (LADG). We also discuss the strategy of surgical management for gastric carcinoids.

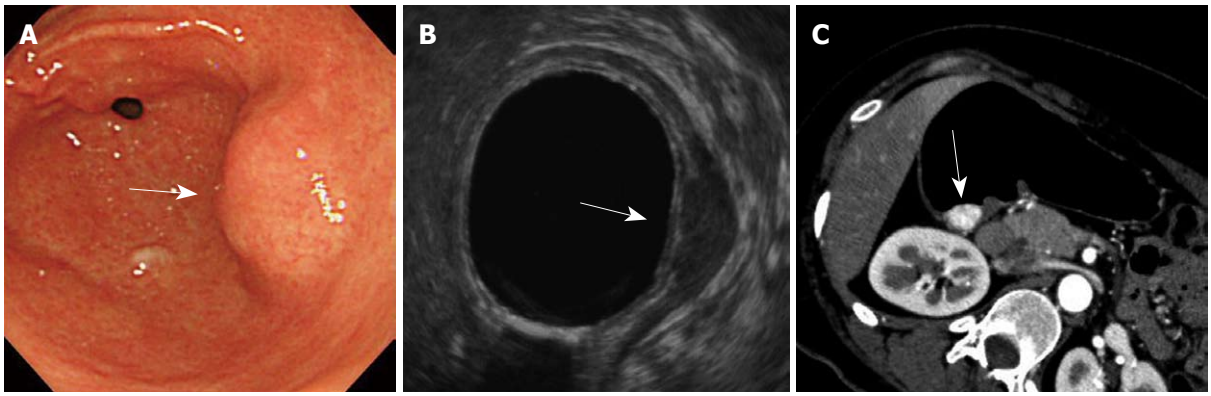

Figure 1 Endoscopy, endoscopic ultrasound and computed tomography findings of the patient. A: Endoscopy revealed a submucosal tumor (arrow) without central depression on the posterior of the antrum; B: Endoscopic ultrasound revealed a tumor (arrow) arising from the muscle layer; C: Computed tomography scan showed the tumor (arrow) stained in the early phase.

CASE REPORT

A 38-year old asymptomatic woman was referred to our hospital for evaluation of a submucosal tumor of the stomach. Gastroendoscopy showed a solitary submucosal tumor without ulceration or central depression on the posterior wall of the antrum (Figure 1A) with no atrophic gastritis. The surface of the tumor was covered completely by intact normal mucosa and biopsy specimens were not able to identify the tumor cells. Endoscopic ultrasound revealed the tumor, nearly 2 cm in diameter, arising from the muscle layer (Figure 1B). A computed tomography scan showed the tumor enhanced in the arterial phase (Figure 1C) and no tumors in other organs such as the liver or lung. Diagnosis could not be confirmed but a gastrointestinal stromal tumor was highly suspected according to these findings. For definitive diagnosis, laparoscopic wedge resection was performed with the assistance of peroral endoscopy as described by Hiki *et al*[8]. The tumor was excised manually using ultrasonic scissors and electrocautery and sutured manually. The operation time was 217 min and blood loss was 5 g. The postoperative course of the initial surgery was uneventful. Pathologically, the tumor was shown to be gastric carcinoid 13 mm × 12 mm in size and with a negative margin. The tumor was capsulated and localized mainly in the submucosal layer and had infiltrated the muscle layer. The mucosa and muscularis mucosa were intact (Figure 2). Microscopically, the tumor was uniform in shape and arranged in cribriform nests (Figure 3A). Immunological staining showed that it was positive for chromogranin A (Figure 3B) and synaptophysin, slightly positive for P53 (Figure 3C) and the Ki-67 labeling index was 10% (Figure 3D). Lymphovascular invasion was not seen. Laboratory tests showed that serum gastrin levels were within the normal range (74 pg/mL). The patient had no other tumors associated with multiple endocrine neoplasia. The patient was diagnosed with a sporadic gastric carcinoid tumor infiltrating the muscle layer, indicating the possibility of lymph node metastasis. For clearance of the regional lymph nodes and radical treatment, LADG was performed with Billroth-I reconstruction

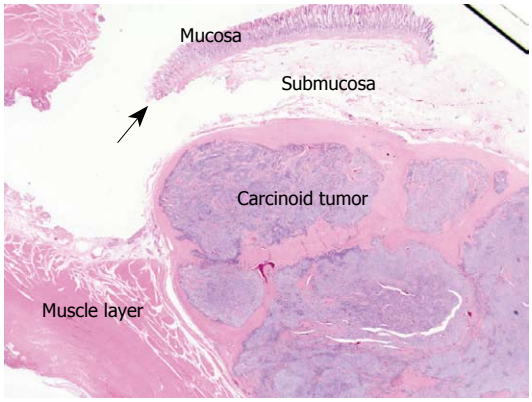

Figure 2 Resected specimen viewed using low magnification. The carcinoid tumors were located in the submucosal layer infiltrating the muscle layer. The muscularis mucosa (arrow) was intact.

with D1+beta lymphadenectomy according to the classification of the Japanese Classification of Gastric Cancer (second English edition)[9] 3 wk after the initial surgery. The required incisions were a 50 mm mini-laparotomy in the epigastrium and another five 5-12 mm for trocar insertion. The operation time was 231 min and blood loss was 40 g. The postoperative course did not have any major complications but there was infection of the mini-laparotomy wound. Finally, pathological examination revealed no metastasis in 18 harvested lymph nodes and no residual tumor. The patient was followed up for 8 mo without findings indicative of recurrence or distant metastasis.

DISCUSSION

Gastric carcinoids arise from proliferating enterochromaffin-like cells of the fundus[10]. Rindi *et al*[3] classified gastric carcinoids into the following three subtypes based on their clinicopathological features as follows: (1) those that arise in a background of type A gastritis; (2) those associated with Zollinger-Ellison syndrome, usually combined with multiple endocrine neoplasia type 1; and (3) those that occur sporadically without hypergastrinemia. Among them,

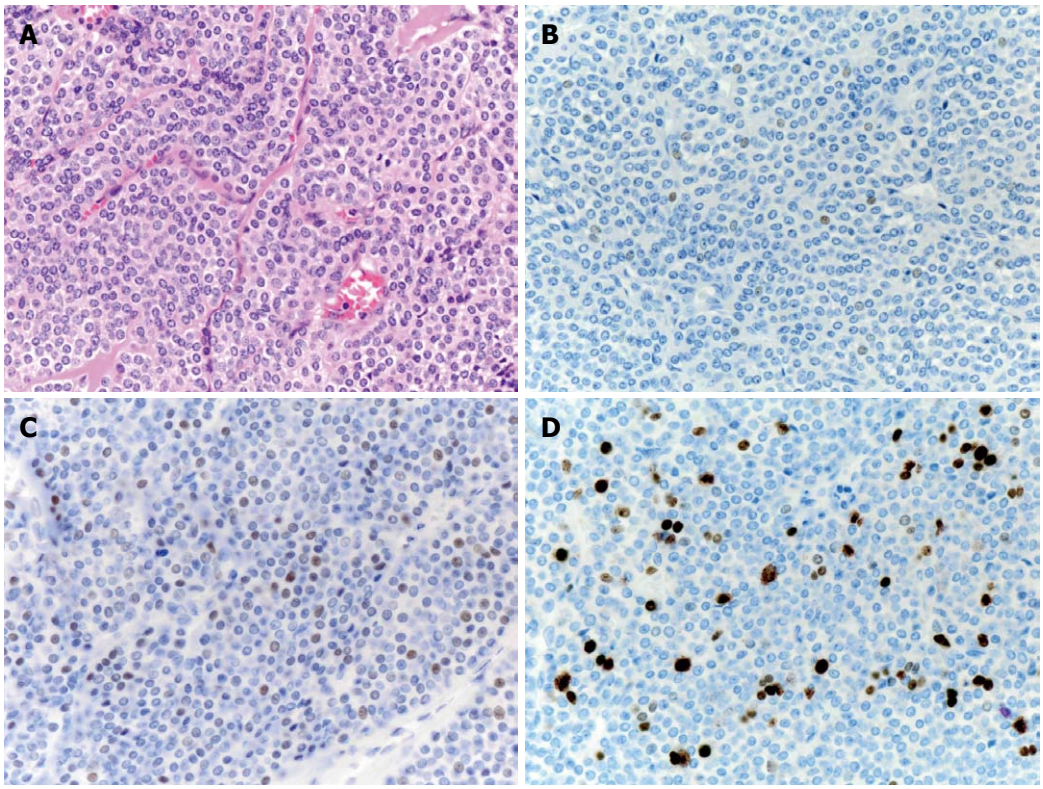

Figure 3 Pathological findings of the resected carcinoid (× 40). A: Hematoxylin and eosin; B: Chromogranin A staining; C: P53 staining; D: Ki-67 staining.

type Ⅲ which are sporadic carcinoids, tend to be solitary, larger, invasive and more often metastatic.

The proportional rates of types Ⅰ, Ⅱ and Ⅲ have been reported as 68%-83%, 0%-8% and 11%-23%[1-6] respectively. The rates of lymph node metastasis of each subtype have been reported to be 0%-7%, 0%-12% and 17%-58%[1-6] respectively which demonstrates a close relationship between the classification of subtypes and malignant potential. Soga[11] reported a statistical evaluation of 1094 cases of gastric carcinoids worldwide and noted that the behavior of gastric carcinoids is correlated with its size and infiltrating depth. In this previous study, the rates of metastasis by size in diameter were 8.2% (< 10 mm), 13.2% (11-20 mm) and 44.8% (> 20 mm)[11]. However, several case reports have shown that type Ⅲ carcinoids of less than 10mm cause lymph node metastasis[12-14] which suggest that some types of type Ⅲ gastric carcinoids possess considerable malignant potential, regardless of their size. The rates of metastasis by infiltrating depth have been reported to be 7.5% (mucosa), 13.2% (submucosa) and 44.8% (muscle layer)[11]. Therefore, management of gastric carcinoids should be determined taking into consideration these previous findings. In the present case, laparoscopic wedge resection revealed the tumor as a type Ⅲ carcinoid that infiltrated the muscle layer which suggested a high possibility of lymph node metastasis. Pathological examination showed no atypical histology but the Ki-67 labeling index was 10% and p53 was slightly positive which suggested a moderate potential of tumor proliferation. Considering these results, we decided that radical surgery was necessary for lymph node clearance. Although there was no lymph node metastasis, we believe that this management was appropriate.

Definitive preoperative diagnosis of gastric submucosal tumors is frequently difficult, such as in the present case. Studies on experimental animals have demonstrated that carcinoids originate in the lower portion of the gastric glands and invade through the muscularis mucosae down to the submucosal layer, then forming a nodule larger than the original portion of the mucosa[15]. In most gastric carcinoids, the tumor simultaneously invades upward to the mucosal layer intraluminally, resulting in central depression. Interestingly, in the present case, not only the mucosa but also the muscularis mucosa was intact and there was a distance between the muscularis mucosa and the tumor capsule (Figure 2) which is unusual with gastric carcinoids. For this reason, the tumor appeared as the usual "submucosal tumor". It is difficult to explain this phenomenon. One possibility is that, in the present case, the tumor may have originated from enterochromaffin-like cells in the heterotopic submucosal gastric gland[16]; however, it is difficult to determine this. Indeed, there were no diffuse heterotopic submucosal cysts in resected specimens of the second operation.

Laparoscopic wedge resection for the diagnosis and treatment of gastric submucosal tumors has been previously employed and its efficacy has been established[17-19]. En-bloc excision of the tumor with intact surrounding tissue allows precise pathological examination, resulting in an accurate assessment for the necessity of additional intervention. Our strategy is that gastric submucosal tumors larger than 2 cm should be laparoscopically removed,

considering the possibility of gastrointestinal stromal tumors, and tumors less than 2 cm can be observed if there is no growing tendency or ulceration. Furthermore, in the present case, LADG with lymph node dissection was performed as a completion surgery. LADG is being increasingly performed in Eastern countries[20] where there are high incidences of early gastric cancer. Its feasibility, acceptable oncological outcomes and contribution to the patient's quality of life have been previously reported. In our department, LADG has been mainly performed in the treatment of early-stage gastric cancer located in the middle or lower portion of the stomach; we have currently experienced over 250 cases. The laparoscopic approach generally provides fewer postoperative adhesions. In the present case, the second operation was able to be performed safely under laparoscopy because postoperative adhesions were minimal and only slight adhesions between the stomach and the pancreas were recognized.

In summary, we describe a case of a sporadic gastric carcinoid tumor, corresponding to Rindi's type Ⅲ, treated by two-stage laparoscopic surgery. Such management can be applied to patients in whom definitive diagnosis is difficult preoperatively. These less invasive surgeries may contribute to the quality of life of patients with gastric cancer and endocrine neoplasms.

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World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
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World J Gastrointest Surg 2010 November 27; 2(11): I
ISSN 1948-9366 (online)

Acknowledgments to reviewers of *World Journal of Gastrointestinal Surgery*

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Gastrointestinal Surgery*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

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World J Gastrointest Surg 2010 November 27; 2(11): I
ISSN 1948-9366 (online)

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The Venetian And Palazzo, 3355 Las Vegas Blvd South, Las Vegas, United States
http://www.gilearn.org/clinical-congress

January 27-31, 2010
Alpine Liver & Pancreatic Surgery Meeting
Carlo Magno Zeledria Hotel, Madonna di Campiglio, Italy
http://www.alpshpbmeeting.soton.ac.uk

February 25, 2010
Multidisciplinary management of acute pancreatitis symptoms
The Royal Society of Medicine, 1 Wimpole Street, London, United Kingdom
http://www.rsm.ac.uk/academ/pancreatitis10.php

March 4-7, 2010
2010 Annual Meeting of the Society of Surgical Oncology
Renaissance® St. Louis Grand Hotel, 800 Washington Avenue, St. Louis, Missouri, United States
http://www.surgonc.org/

March 25-28, 2010
20th Conference of the Asian Pacific Association for the Study of the Liver
Beijing, China
http://www.apasl2010beijing.org/en/index.aspx

April 14-18, 2010
The International Liver Congress™ 2010
Vienna, Austria

May 1-5, 2010
2010 American Transplant Congress
San Diego Convention Center, 111 West Harbor Drive, San Diego, United States
http://www.atcmeeting.org/2010

May 1-5, 2010
Digestive Disease Week 2010
Ernest N Morial Convention Center, 900 Convention Center Blvd, New Orleans, United States
http://www.ddw.org/

May 15-19, 2010
Annual Meeting of the American Society of Colon and Rectal Surgeons
Hilton Minneapolis Hotel & Convention Center, Minneapolis, Minnesota, United States
http://www.fascrs.org/

September 16-18, 2010
Prague Hepatology Meeting 2010
Prague, Czech Republic
http://www.congressprague.cz/en/kongresy/phm2010.html

September 23-25, 2010
2010 Gastrointestinal Oncology Conference
The Sheraton Philadelphia City Center, Philadelphia, United States
http://www.isgio.org/isgio2010/program.htm

October 20-23, 2010
Australian Gastroenterology Week
Melbourne, Australia
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November 13-14, 2010
Case-Based Approach to the Management of Inflammatory Bowel Disease
San Francisco, United States

WJGS World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2010 November 27; 2(11): I-V
ISSN 1948-9366 (online)

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-diarrhoea. *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.0000035706.28494.09]

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. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary 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. Wieczorek 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 ± SD or mean ± 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 υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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