Cancer Chemother Pharmacol (2014) 73:97–102
DOI 10.1007/s00280-013-2323-6

ORIGINAL ARTICLE

Phase II clinical study of alternate-day oral therapy with S-1 as first-line chemotherapy for locally advanced and metastatic pancreatic cancer

Hiroki Yamaue · Sohei Satoi · Takamasa Kanbe · Motoki Miyazawa · Masaji Tani · Manabu Kawai · Seiko Hirono · Kenichi Okada · Hiroaki Yanagimoto · A-Hon Kwon · Tomoyuki Mukouyama · Hiroaki Tsunoda · Kazuo Chijiiwa · Jiro Ohuchida · Jun Kato · Kazuki Ueda · Taketo Yamaguchi · Shinichi Egawa · Kazuhiko Hayashi · Tetsuhiko Shirasaka

Received: 26 May 2013 / Accepted: 10 October 2013 / Published online: 22 October 2013

Abstract
Purpose Based on the results of first-line chemotherapy for advanced pancreatic cancer, S-1 was confirmed to be non-inferior to gemcitabine. However, the recommended regimen of 4 weeks of administration followed by 2 weeks of drug withdrawal frequently causes adverse effects. On the other hand, we experienced in clinical practice that alternate-day administration of S-1 reduced adverse effects and were tolerable for advanced pancreatic cancer patients unwilling to continue the standard daily administration. We therefore conducted a multicenter cooperative prospective study to compare daily with alternate-day administration of S-1 for advanced pancreatic cancer.
Methods Patients with advanced pancreatic cancer were eligible for enrollment in this trial. S-1 was administered at a dose of 40–60 mg twice daily, calculated according to body surface area, on Monday, Wednesday, Friday, and Sunday. Each treatment cycle was 42 days. The primary end point was overall survival (OS). Secondary end points were safety, response rate (RR), progression-free survival (PFS), and time to treatment failure (TTF).
Results Forty-eight patients were evaluable for response. OS as the primary end point was 8.4 months (95 % CI 5.4–10.8), and the 1-year survival rate was 29.2 %. PFS was 5.5 months, and TTF was 3.9 months. RR was 10.4 %, and the disease control rate was 79.2 %. Grade 3/4 hematological and non-hematological toxicities were minor. All of these adverse reactions were tolerable and reversible.
Conclusions The current data demonstrate the mitigation of adverse effects with alternate-day administration of

H. Yamaue (✉) · M. Miyazawa · M. Tani · M. Kawai · S. Hirono · K. Okada · J. Kato
Second Department of Surgery, Wakayama Medical University, 10-31 Kimiidera, Wakayama City, Wakayama 641-8510, Japan
e-mail: yamaue-h@wakayama-med.ac.jp

S. Satoi · H. Yanagimoto · A.-H. Kwon
Department of Surgery, Kansai Medical University, Moriguchi, Japan

T. Kanbe · T. Mukouyama · H. Tsunoda
Department of Internal Medicine, San-in Rosai Hospital, Yonago, Japan

K. Chijiiwa · J. Ohuchida
Department of Surgical Oncology and Regulation of Organ Function, Miyazaki University School of Medicine, Miyazaki, Japan

K. Ueda
Second Department of Internal Medicine, Wakayama Medical University, Wakayama, Japan

T. Yamaguchi
Department of Gastroenterology, Chiba Cancer Center, Chiba, Japan

S. Egawa
Department of Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan

K. Hayashi
Department of Chemotherapy and Palliative Care, Tokyo Women's Medical University, Tokyo, Japan

T. Shirasaka
Kitasato Institute for Life Science, Kitasato University, Tokyo, Japan

S-1, and this appears to be a more sustainable option for advanced pancreatic cancer.

Keywords Alternate-day · Oral therapy · S-1 · Chemotherapy · Pancreatic cancer

Introduction

Pancreatic cancer is known for its most unfavorable prognosis, with a 5-year survival rate of approximately 9 % [1]. Surgery is the only treatment expected to completely eradicate the condition, but 80 % of patients are diagnosed with the cancer when they have already reached an inoperable status. For unresectable patients, chemotherapy is commonly used, and since Burris et al. [2] demonstrated the significant efficacy of gemcitabine (GEM) in prolonging life expectancy over 5-fluorouracil (5-FU) in a comparative study conducted in 1997, GEM has become the major chemotherapeutic agent; yet the median survival time (MST) of unresectable patients treated with GEM remains 5–7 months, suggesting that its effect on survival is inadequate. In Japan, a tegafur/gimeracil/oteracil combination capsule (S-1) is used to treat various types of cancers, and a domestic late phase II trial to evaluate S-1 in patients with pancreatic cancer showed that the response rate (RR) was 37.5 %, and the median progression-free survival time (PFS) was 3.7 months [3]. Furthermore, phase III studies (GEST study) of GEM + S-1 combination therapy (GS therapy), GEM, and S-1 were conducted in Japan and Taiwan in patients with unresectable advanced pancreatic cancer, and a controlled trial of the effects of GEM versus S-1 on survival showed that the hazard ratio (HR) was 0.96 (97.5 % confidence interval [CI] 0.78–1.18), demonstrating the non-inferiority of S-1 to GEM [4]. The standard regimen of S-1 treatment used in the GEST study, a 4-week daily administration followed by a 2-week rest period, has frequently been associated with digestive symptoms such as anorexia, diarrhea, and stomatitis, which can result in a need to discontinue treatment altogether. It is still unclear, however, whether the therapeutic efficacy of modified regimens with reduced overall dosage or of shortened treatment cycles is as effective as the standard dosage regimens in patients reporting adverse events with S-1. In recent years, an alternate-day administration of S-1 has been reported to alleviate adverse reactions without reducing the efficacy of treatment. Arai et al. [5] started treatment for 92 patients with advanced recurrent gastric cancer with a schedule of administration for 4 consecutive weeks followed by a 2-week rest period, but later switched to an alternate-day regimen for 72 patients, upon their own request, in whom the therapy had to be interrupted due to grade 1 or higher non-hematological toxicities (31.5 %). As a result, the number of patients with grade 2 or higher non-hematological toxicities dropped remarkably to 2 (2.8 %), and the average duration of therapy for the alternate-day regimen was extended to 272 days, as opposed to 47 days with daily administration. In the study, time to progression (TTP) was 170 days, MST was 11 months, and the disease control rate in the evaluable patients was reported to be 53 % (31/58). Since we have observed the reduction in adverse events and the long-term administration rendered possible by replacing the S-1 regimen with an alternate-day administration, we also conducted a clinical phase II study of alternate-day S-1 administration for the treatment of advanced recurrent pancreatic cancer in an attempt to alleviate adverse reactions and to achieve long-term administration.

Patients and methods

Eligibility

The eligibility criteria for patients were as follows: pancreatic cancer with adenocarcinoma or adenosquamous cancer confirmed by histological testing; locally advanced and metastatic pancreatic cancer; a measurable lesion; ultrasonography examination taken 28 days prior to enrollment; no prior treatments (radiotherapy, chemotherapy, or immune therapy) other than resection of pancreatic cancer; patients in whom pre- and postoperative adjuvant chemotherapy had been administered were eligible if recurrence was confirmed 24 weeks after the final administration (or after day 169 counting from the day following the termination of treatment); patient age between 20 and 80 years; 0 or 1 ECOG performance status (PS); patients with the principal organ functions sufficiently maintained (see criteria below); orally administrable; no abnormal findings leading to clinical complications confirmed by electrocardiogram (ECG) taken within 28 days (4 weeks) of enrollment; and cases in which a patient's written consent had been obtained. The following criteria were used to define whether principal organ functions were sufficiently maintained, from laboratory data taken within 14 days of enrollment (tests conducted on the same day as the enrollment day 2 weeks prior were acceptable): white cell count >3,500/mm^3; neutrophil count >2,000/mm^3; hemoglobin >9.0 g/dL; blood platelet count >100,000/mm^3; total bilirubin <2.0 mg/dL; AST/ALT <150 IU/L; serum creatinine <1.2 mg/dL; and creatinine clearance >60 mL/min.

Treatment

The appropriate dose of S-1 was calculated as follows: patients with a body surface area of <1.25, 1.25–1.50, and >1.5 m^2 received daily doses of 80, 100, and 120 mg/day,

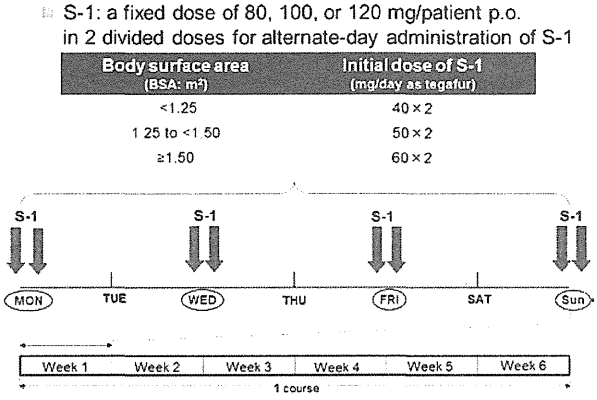

Fig. 1 Treatment schedule for alternate-day with S-1

respectively, administered orally in two equal amounts, after breakfast and after the evening meal. The initial dose of S-1 was administered either on a Monday, Wednesday, Friday, or Sunday (the specified days). S-1 was then administered according to the schedule for the alternate-day regimen for a cycle of 6 weeks. The first day of S-1 treatment was defined as day 1. The first dose of S-1 was taken after the evening meal if it could not be taken after breakfast. The day on which the first dose was administered was designated as day 1 even if the initial dose was taken after the evening meal. The second dose was then taken on the following specified day (e.g., if the initial dose was administered on Friday evening, the next dose would be taken on the following Sunday morning). S-1 administration was continued on Mondays, Wednesdays, Fridays, and Sundays until any one of the criteria for terminating the regimen was satisfied (Fig. 1). The days specified for administering S-1 could not be altered. No missed doses could be taken on days other than those initially prescribed. A dose reduction of 20 mg/day was recommended if grade 3 or higher hematological or non-hematological toxicity occurred in the previous cycle; dose re-escalation was not allowed. Patients who required more than 4 weeks of rest for recovery from any toxicity other than nausea, vomiting, or anemia, or who required a dose reduction of >20 mg/day, were withdrawn from the study.

Evaluation

Assessment of the response rate (RR) was carried out using the sum of complete (CR) and partial response (PR) rates. The antitumor efficacy was interpreted in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and evaluated according to the following criteria: The maximum response rate obtained for each patient by the final course was designated as the response rate of the patient, thereby making the confirmation of 4-week sustained efficacy unnecessary. The efficacy evaluation was carried out for all eligible cases. The number of non-evaluable cases was added only to the denominator of the efficacy evaluation. Stable disease (SD) referred to a stable condition in which none of the other conditions, that is, progressive disease (PD) confirmed CR, and confirmed PR, applied throughout the 6-week cycle. Adverse event nomenclature, grades, and dates of onset were recorded in the follow-up report forms by the participating physicians. The evaluation of adverse event grades and nomenclature were recorded according to the CTCAE v4.0. Overall survival (OS) and the secondary end points, progression-free survival (PFS), and time to treatment failure (TTF) were calculated using the Kaplan–Meier method.

Statistics

The primary end point was OS, and the secondary end points were PFS, TTF, RR, and the frequency and severity of adverse events. Forty-five patients were required, based on the assumption of an expected OS of 6 months and a threshold of 4 months, with an α-error of 0.05 and a β-error of 0.2. In order to allow for patients who were ineligible or who subsequently dropped out, it was planned that 50 patients would be included in this study.

Results

Patients

During the period from August 2009 to May 2011, a total of 50 patients were enrolled from 13 different institutions. Two of these patients did not meet the eligibility criteria: One was excluded due to the patient's refusal and the other on the grounds of inadequate renal function. The baseline characteristics of the patients are shown in Table 1.

Treatment

The 48 patients received a total of 99 cycles of chemotherapy, with a median number of cycles of 2.6 (range 1–12). The dose of S-1 was reduced in one patient because of grade 3 anorexia and fatigue. The median relative dose intensity for the population was 98.9 %, indicating that patient compliance with S-1 chemotherapy was good. Reasons for withdrawal of treatment were progressive disease (79.2 %), patient's refusal (10.4 %), and adverse events (8.3 %). After discontinuation of alternate-day therapy, 14 patients (29.2 %) received GEM-based chemotherapy, 3 patients (6.2 %) received S-1-based chemotherapy, 3 patients (6.2 %) received GEM + S-1 chemotherapy, and 28 patients (58.3 %) received supportive care.

Table 1 Patient characteristics

Characteristic	Number (%)
Age (year)	
Median	67
Range	34–75
Sex	
Male	21 (44)
Female	27 (56)
Performance status	
0	40 (83)
1	8 (17)
Extent disease	
Locally advanced	11 (23)
Metastatic	37 (77)
Metastatic sites	
Liver	21 (44)
Peritoneum	10 (21)
Distant lymph nodes	6 (13)
Lung	1 (2)

Toxicity

The most common adverse events are listed in Tables 2 and 3. The only grade 3 or higher hematotoxicities reported were neutropenia (4.2 %) and cholecystitis (2.0 %), and most other instances remained below grade 2 (<30 %). Furthermore, the only grade 3 or higher non-hematotoxicities reported were anorexia and general malaise (2.0 %), and most of these adverse events were also below grade 2 (<20 %). Although gastrointestinal toxicities and myelosuppression were frequently observed with standard treatment, alternate-day treatment was manageable with appropriate medical care. There was no incidence of treatment-related death.

Table 4 Patient characteristics in relation to the response

Variable	Number (%)
Complete response	0 (0.0)
Partial response	5 (10.4)
Stable disease	33 (68.8)
Progressive disease	10 (16.6)
Objective response rate (%)	5 (10.4)
95 % CI	(3.5–22.7)
Disease control rate (%)	38 (79.2)
95 % CI	(65.0–89.5)

Response and survival

The antitumor effect is shown in Table 4. The objective response rate was 10.4 % (95 % CI 3.5–22.7 %), and the disease control rate was 79.2 % (95 % CI 65.0–89.5 %). At the median follow-up interval of 24 months, 3 patients were still alive and censored. The median overall survival time was calculated for all 48 patients: OS was 8.4 months (95 % CI 5.4–10.8), the one-year survival rate was 29.2 %, and PFS was 5.5 months. Time to treatment failure (TTF) was 3.9 months (95 % CI 2.6–7.3). The Kaplan–Meier survival curve is shown in Figs. 2, 3, and 4.

Discussion

While the results obtained in GEST showed that S-1 monotherapy was one of the standard therapeutic modalities

Table 2 Hematological toxicities

Event	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	≧Grade 3 (%)
Leukopenia	7 (14.6)	5 (10.4)	0 (0.0)	0 (0.0)	0 (0.0)
Neutropenia	4 (8.3)	1 (2.0)	2 (4.2)	0 (0.0)	2 (4.2)
Thrombocytopenia	6 (12.5)	8 (16.6)	0 (0.0)	0 (0.0)	0 (0.0)
Anemia	5 (10.5)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total bilirubin increased	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST increased	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 3 Non-hematological toxicities

Event	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	≧Grade 3 (%)
Anorexia/fatigue	4 (8.3)	5 (10.4)	1 (2.0)	0 (0.0)	1 (2.0)
Mucositis	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	2 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infection	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholecystitis	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (2.0)

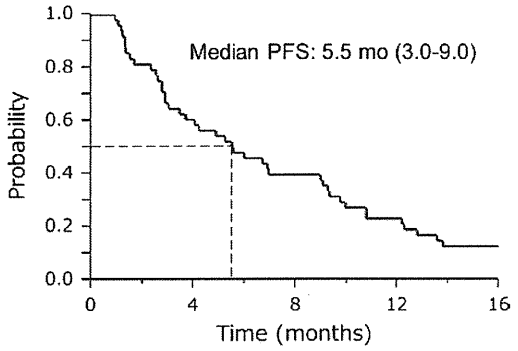

Fig. 2 Kaplan–Meier estimate of progression-free survival according to treatment of S-1

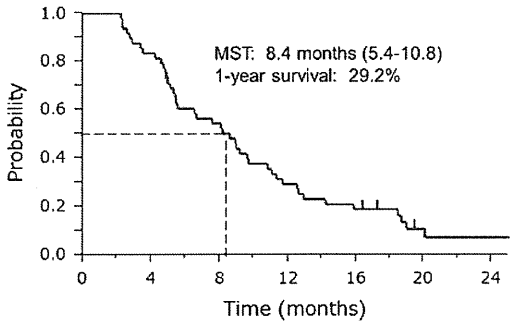

Fig. 3 Kaplan–Meier estimate of overall survival according to treatment of S-1

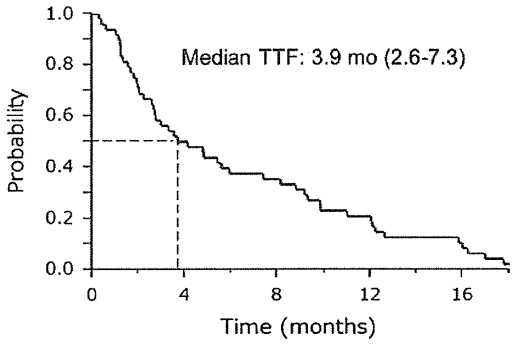

Fig. 4 Kaplan–Meier estimate of time to treatment failure according to treatment of S-1

against advanced pancreatic cancer, there still was room for improvement with respect to the administration schedule, in order to reduce adverse events. At the same time, Lipkin et al. and Clarkson and Ota et al. [6, 7] demonstrated a significant difference between the cell cycles of a host's normal cells and cancer cells. The cell cycle of the normal cells was determined to be half to 1 day, and the length of S phase in which 5-FU was activated was 12 h. In contrast, the cell cycle of cancer cells was 4–5 days, and their S phase lasted for more than 24 h. Thus, by taking advantage of the difference in the cell cycles, a clinically optimum dosage regimen for 5-FU could be ascertained. If a reasonable number of normal cells were to avoid exposure to 5-FU (by means of a 1 day cessation of 5-FU treatment), it could be possible to avoid some of the toxic effects of 5-FU on the normal cells of the intestinal mucosa. In addition, because not only was the cell cycle of cancer cells longer (4–5 days), but also their S phase lasted for more than 24 h, Shirakawa et al. [8] argued that the alternate-day regimen for S-1 would not diminish the cytotoxic effects against cancer cells even if 5-FU were repeatedly activated every other day with a drug cessation period in between. Moreover, Arai et al. [9] treated gastric cancer cell lines with the same total dose of S-1 on alternate or consecutive days to compare these regimens. Although it was a basic study, the results demonstrated that alternate-day treatment with S-1 was equivalent to consecutive-day treatment in terms of the relative inhibition of tumor growth, but with lower toxicity. Furthermore, Sakuma et al. conducted a retrospective examination of the alternate-day regimen in 266 patients with gastric cancer (including advanced recurrent cancer and postoperative adjuvant chemotherapy). The results obtained in the study showed that the efficacy of the regimen was by no means inferior to that of the standard regimen, and with respect to the incidence of adverse events for each grade, extremely favorable results were obtained as follows: 0 % grade 3 or higher, 6 % grade 2, and 7.5 % grade 1 [10].

In this phase II study, the MST was 8.4 months, 1-year overall survival rate was 29.2 %, PFS was 5.5 months, and TTF was 3.9 months. Seven cases of grade 2 or higher non-hematotoxicities (14.6 %), and two cases of grade 3 or higher hematotoxicities (4.2 %) were reported; therefore, the efficacy and safety of the regimen have been confirmed. Although a high response rate was not obtained with S-1 alternate-day administration in this study, the disease control rate was approximately 80 %, and the frequency of adverse events was noticeably less compared to that of the 4-week S-1 regimen followed by a 2-week rest period [3, 4]. The transition to a second-line therapy was not specified in this study; however, these data were recorded as follows. The percentage of patients who underwent transition to GEM, S-1, or GEM + S-1 therapy, or to no further treatment was 29.2, 6.2, 6.2, and 58.3 %, respectively; in total, the percentage of patients undergoing transition to second-line treatment in this study was lower than the percentage undergoing transition to second-line treatment with GEM or GEM + S-1 in the GEST study (approximately 70 %). The fact that in 60 % of patients given the S-1 alternate-day regimen, the second-line treatment could not be

administered due to worsening of the overall health status induced by the first-line treatment has suggested that there is still room for improvement in the treatment efficacy/route of administration of first-line treatment for pancreatic cancer.

Therefore, by comparison with the standard regimen, the S-1 alternate-day regimen may have superior tolerability as well as continuity in the treatment for advanced recurrent gastric cancer or unresectable advanced pancreatic cancer. Compared to other types of carcinoma, unresectable advanced pancreatic cancer has been associated with a higher frequency of serious adverse events when treated with S-1; the alternate-day administration schedule of S-1 therefore has promising potential for not only making treatment more patient-friendly by alleviating side effects, but also achieving improvements in compliance and treatment outcomes [4, 11, 12].

In conclusion, from the results obtained in this study, we have designed and are conducting a randomized phase II study confirming non-inferiority, in terms of overall survival, of the alternate-day regimen for S-1, which has been suggested to result in superior safety and continuity and comparing safety and health-related quality of life in the standard and alternate-day regimens (PAN-01, UMIN000008604). The objective is to determine a standard treatment method necessary to conduct a superiority analysis for developing novel treatment approaches in the future. Furthermore, this research will facilitate the much-awaited development of combination chemotherapy maintaining the efficacy of each individual drug, by applying the alternate-day regimen, which promises fewer side effects, as a basic treatment.

References

1. Jemal A, Bray F, Center MM et al (2011) Global center statistics. CA Cancer J Clin 61:69–90
2. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 15:2403–2413
3. Okusaka T, Funakoshi A, Furuse J, Boku N, Yamao K, Ohkawa S, Saito H (2008) A late phase II study of S-1 for metastatic pancreatic cancer. Cancer Chemother Pharmacol 61:615–621
4. Ueno H, Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, Boku N, Fukutomi A, Sugimori K, Baba H, Yamao K, Shimamura T, Sho M, Kitano M, Cheng AL, Mizumoto K, Chen JS, Furuse J, Funakoshi A, Hatori T, Yamaguchi T, Egawa S, Sato A, Ohashi Y, Okusaka T, Tanaka M (2013) Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. J Clin Oncol 31(13):1640–1648
5. Arai W, Hosoya Y, Hyodo M, Yokoyama T, Hirashima Y, Yasuda Y, Nagai H, Shirasaka T (2004) Alternate-day oral therapy with TS-1 for advanced gastric cancer. Int J Clin Oncol 9:143–148
6. Lipkin M, Sherlock P, Bell B (1963) Cell proliferation kinetics in the gastrointestinal tract of man. II. Cell renewal in stomach, ileum, colon, and rectum. Gastroenterology 45:721–729
7. Clarkson B, Ota K, Ohkita T, O'Connor A (1965) Kinetics of proliferation of cancer cells in neoplastic effusions in man. Cancer 18:1189–1213
8. Shirasaka T (2009) Development history and concept of an oral anticancer agent S-1 (TS-1): its clinical usefulness and future vistas. Jpn J Clin Oncol 39:2–15
9. Arai W, Hosoya Y, Haruta H, Kurashina K, Saito S, Hirashima Y, Yokoyama T, Zuiki T, Sakuma K, Hyodo M, Yasuda Y, Nagai H, Shirasaka T (2008) Comparison of alternate-day versus consecutive-day treatment with S-1: assessment of tumor growth inhibition and toxicity reduction in gastric cancer cell lines in vitro and in vivo. Int J Clin Oncol 13:515–520
10. Sakuma K, Hosoya Y, Arai W, Haruta H, Ui T, Kurashina K, Saito S, Hirashima Y, Yokoyama T, Zuiki T, Hyodo M, Nagai H, Yasuda Y, Shirasaka T (2010) Alternate-day treatment with S-1 in patients with gastric cancer: a retrospective study of strategies for reducing toxicity. Int J Clin Oncol 15:166–171
11. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H, Takeuchi M (2008) S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 9:215–221
12. Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, Koizumi W, Saito H, Yamaguchi K, Takiuchi H, Nasu J, Ohtsu A; Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group (2009) Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol 10:1063–1069

J Hepatobiliary Pancreat Sci (2014) ••:••–••
DOI: 10.1002/jhbp.92

ORIGINAL ARTICLE

Proposal of a new staging system for mass-forming intrahepatic cholangiocarcinoma: a multicenter analysis by the Study Group for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery

Takahiro Uenishi · Shunichi Ariizumi · Taku Aoki · Tomoki Ebata · Masayuki Ohtsuka · Eiichi Tanaka · Hiroshi Yoshida · Satoru Imura · Masaki Ueno · Norihiro Kokudo · Masato Nagino · Satoshi Hirano · Shoji Kubo · Michiaki Unno · Mitsuo Shimada · Hiroki Yamaue · Masakazu Yamamoto · Masaru Miyazaki · Tadahiro Takada

T. Uenishi · S. Kubo
Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan

M. Yamamoto (✉) · S. Ariizumi
Department of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University, 1-4-3 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan
e-mail: yamamoto@ige.twmu.ac.jp

T. Aoki · N. Kokudo
Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Tokyo University Graduate School of Medicine, Tokyo, Japan

T. Ebata · M. Nagino
Division of Surgical Oncology, Department of Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

M. Ohtsuka · M. Miyazaki
Department of General Surgery, Chiba University Graduate School of Medicine, Chiba, Japan

E. Tanaka · S. Hirano
Department of Surgical Oncology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

H. Yoshida · M. Unno
Division of Hepato-Biliary-Pancreatic Surgery, Department of Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan

S. Imura · M. Shimada
Department of Surgery, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima, Japan

H. Yamaue · M. Ueno
Second Department of Surgery, Wakayama Medical University, Wakayama, Japan

T. Takada
Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan

Abstract

Background Recently, the Liver Cancer Study Group of Japan (LCSGJ) staging system for intrahepatic cholangiocarcinoma (ICC) was followed by a proposal of the American Committee on Cancer (AJCC)/International Union Against Cancer (UICC) system. The present study aimed to assess the accuracy of both systems to predict survival after curative resection for mass-forming ICC and to establish a new staging system based on survival analysis results. The present study was conducted as a project study of the Japanese Society of Hepato-Biliary-Pancreatic Surgery.

Methods Clinical data from 233 patients who underwent curative resection for mass-forming ICC were retrospectively reviewed. Survival analysis was performed to identify predictors of postoperative outcomes, and a new staging system was established. The survival stratification of our proposed system was compared with two previous staging systems.

Results A N0M0 cohort analysis demonstrated that tumor size, tumor number, and vascular invasion were independently associated with survival after curative resection for mass-forming ICC, whereas serosal and periductal invasion were not. Of patients with nodal metastases, patients with T4 tumor had significantly lower overall survival rate than patients with T1, T2, or T3 tumor. Thus, we proposed a new staging system as follows: serosal invasion was excluded from the LCSGJ T categories, and patients with nodal metastases were divided into stage IVA or IVB according to T classification. The new system better stratified survival after curative resection for mass-forming ICC than the two previous systems.

Conclusions The AJCC/UICC staging system failed to stratify the Japanese patients with mass-forming ICC. The new staging system provided better survival prediction in the patients who underwent curative resection for mass-forming ICC, although further studies are necessary to evaluate the impact of tumor size on survival.

Keywords Mass-forming intrahepatic cholangiocarcinoma · Postoperative outcomes · Tumor-node-metastasis classification

Introduction

Intrahepatic cholangiocarcinoma (ICC), which arises from the second-order or more peripheral branches of the biliary tree, is the second most common primary liver cancer after hepatocellular carcinoma (HCC). A recent nationwide survey in Japan indicated that ICC accounts for approximately 4% of all primary liver cancers [1]. However, over the past 3 decades, a worldwide increase in the ICC incidence and associated mortality rates have been reported, even in low prevalence regions [2–4]. Despite improvements in imaging studies, surgical procedures, and perioperative management, the postoperative outcome in patients with ICC remains unsatisfactory, as the 5-year overall survival rate after potentially curative resection is 30–40% [5–17]. Recently, some investigators reported that adjuvant gemcitabine-based chemotherapy could be a promising strategy to improve survival after surgical resection for cholangiocarcinoma [18, 19]. A prospective randomized trial should be performed to determine the impact of adjuvant therapy on postoperative outcomes. Therefore, an accurate staging system for ICC is necessary.

Despite distinct differences in the biological behaviors and postoperative outcomes of HCC and ICC, ICC was previously staged according to the tumor node metastasis (TNM) classification of American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) liver cancer staging system, which was based exclusively on data derived from clinical experiences with HCC patients. In 2009, the TNM classification for ICC was independent of that for HCC in the 7th edition of the staging manual published by AJCC/UICC [20], based on the Surveillance, Epidemiology, and End Results (SEER) database of 598 patients who underwent hepatic resection for ICC [21]. In the AJCC/UICC staging system, the T category comprises the tumor number, vascular invasion, visceral peritoneum perforation or extrahepatic direct invasion, and periductal invasion, but not tumor size. In contrast, since 2003, the Liver Cancer Study Group of Japan (LCSGJ) proposed a macroscopic classification and staging system for ICC [22] based on data from 245 patients who underwent liver resection for ICC [23]. The LCSGJ staging system was adapted only to mass-forming (MF) type of ICC and is essentially equal to the HCC staging system, although serosal invasion includes T category factors. In the present study, survival analyses were performed on data from consecutive patients at nine high-volume centers to verify the prognostic accuracy of the AJCC/UICC and LCSGJ staging systems for ICC and to propose a new staging system.

Patients and methods

A retrospective cohort study was performed on a database of 341 consecutive patients who underwent hepatic resection with a curative intent for ICC at the nine medical university hospitals, between January 1995 and December 2004. Patients with hilar (Klatskin) cholangiocarcinoma, mixed HCC and ICC, and bile duct cystadenocarcinoma were excluded from this study cohort. The medical records including hospital charts, operation records, and pathological examination reports were reviewed. All the patients routinely underwent physical examinations and provided clinical histories. Assessments of serum laboratory tests, including hepatitis B surface antigen, hepatitis C virus antibody, carcinoembryonic antigen, carbohydrate 19-9, and liver function tests, were performed. Preoperative diagnoses were based on combined imaging data, including computed tomography, ultrasonography, and/or magnetic resonance imaging. Chest radiography, upper gastrointestinal endoscopy, and colonoscopy were also performed. ICC tumors were classified according to the macroscopic classification proposed by the LCSGJ [22]. Among the 341 patients with ICC, 290 patients had the MF type, 29 had the periductal-infiltrating (PI) type, 22 had the intraductal growth (IG) type. When an ICC tumor was composed of two macroscopic types, the tumor was classified according to the predominant type. The 290 MF-ICC cases included 100 MF+PI cases and seven MF+IG cases. Of the 290 patients with MF-ICC, 251 underwent curative resection. Curative resection was defined as the complete removal of the entire macroscopic tumors without residual tumors. Data from 15 patients (5.6%) who died perioperatively (within 60 days after surgery or during the initial hospitalization) and three patients who were lost to follow-up within 6 months after surgery were also excluded. Finally, 233 patients were enrolled in this cohort study. Data from the last follow-up and vital statuses were collected for the all patients.

Surgical procedure

The operative procedure was described according to the Brisbane 2000 system [24]. A total of 183 patients underwent hemihepatectomy or a more extended resection.

Sectionectomy, segmentectomy, and partial resection were performed in 22, 13, and 15 patients, respectively. Concomitant extrahepatic bile duct and vascular resection with reconstruction were performed in 122 and 34 patients, respectively. Lymph node dissection was not uniformly performed in all the patients owing to the multicenter retrospective nature of the study. Of the 233 patients, 156 patients underwent regional lymph node dissection that extended beyond the hepatoduodenal ligament, including nodes along the common hepatic artery and on the posterior surface of the pancreas head and/or more distal lymph nodes. Additionally, nodes in the cardiac portion and along the lesser curvature of the stomach were dissected when ICC tumor was located in the left hepatic lobe. The remaining 77 patients did not demonstrate nodal metastases in the preoperative imaging study. Of the 77 patients, 27 underwent node sampling in the hepatoduodenal ligament because of suspicious nodal involvement, based on intraoperative findings. Overall, 48 of the 50 patients who underwent liver resection alone had peripheral MF-ICC; the remaining two patients had MF+PI tumor.

Pathological examination

Tumor size was based on the largest tumor dimension of the resected specimens. In cases with multiple tumors, each tumor was histologically confirmed as ICC. Vascular, serosal, and periductal invasion were also confirmed by pathological examinations. Vascular invasion was divided into two subgroups. Major vascular invasion was defined as tumor invasion to the first branch, with or without extension to the trunk of the portal vein, to the hepatic vein trunk and/or the inferior vena cava, or to the left, right, or proper hepatic artery. In the present study, patients who did not undergo lymph node sampling were considered pN0 rather than pNx, although this might have led to understaging.

Statistical analysis

Components of the AJCC/UICC and LCSGJ staging schema were analyzed as variables that could possibly affect prognosis. Survival curves were estimated using the Kaplan–Meier method and were compared with the log-rank test. Potential survival predictors were evaluated in a multivariate analysis using a Cox proportional hazards regression model.

Results

Survival analysis in the N0M0 cohort and survival stratification according to T classification

Initially, the postoperative outcomes were analyzed in 146 patients without lymph node metastases (N0M0 cohort) to determine the T classification components. At the time of analysis, the median follow-up period was 1058 days (range, 81 to 4995 days). The median survival time after curative resection for N0M0 ICC was 1177 days. The overall 3- and 5-year survival rates of the 146 patients were 51.7% and 43.2%, respectively. The pathological features of the N0M0 cohort are shown in Table 1. The survival curves according to tumor size are shown in Figure 1a. The survival rate in the patients with ICC $\leq$ 2 cm was much higher than those of the other groups, but the survival curve of patients with ICC of 2–5 cm was similar to that of the patients with ICC > 5 cm. The tumor number significantly affected the postoperative outcomes (Fig. 1b). Patients with single tumor had a significantly longer survival than those with multiple tumors. However, there was no significant difference in survival between patients with multiple tumors limited to a single hepatic lobe and those with bilobar tumors (P = 0.921). The survival rate in the patients without vascular invasion was also significantly higher than that in the patients with vascular invasion (Fig. 1c), although no difference in survival was noted between major branch and peripheral invasion (P = 0.153). Serosal invasion was not recognized as a significant factor in the univariate analysis. Moreover, in 57 patients without vascular invasion, the survival rates for patients with and without serosal invasion were 68.0% and 63.9% at 3 years and 55.6% and 57.8% at 5 years, respectively. When vascular invasion was absent, the overall survival rates of the patients with serosal invasion were similar to those of the patients without serosal invasion (P = 0.930). The presence of periductal invasion also did not affect the postoperative outcomes. In the multivariate analysis, tumor size >2 cm, vascular invasion, and multiple tumors were independent factors associated with poor postoperative outcomes (Table 1). Based on the results of the multivariate analysis, we stratified the patients into three groups according to the presence of vascular invasion and tumor number. The overall survival rates in the 44 patients with solitary tumor and no vascular invasion, in the 79 patients with either vascular invasion or multiple tumors, and in the 23 patients with both factors were 74.3%, 45.3%, and 28.7% at 3 years and 64.7%, 37.9%, and 14.3% at 5 years, respectively. The survival curves of these three groups were clearly separate, and significant survival differences could be observed between any two of these groups (Fig. 2). However, the overall survival rates in the 66 patients with single tumor and vascular invasion and in the 13 patients with multiple tumors and no vascular invasion were 47.5% and 29.7% at 3 years and 39.4% and 29.7% at 5 years, respectively (P = 0.710). In the present study, the impact of tumor size on survival could not be analyzed within each group according to the presence of vascular invasion and tumor number because none of the patients with ICC $\leq$ 2 cm had multiple tumors. However, a tumor size >2 cm had the

Table 1 Univariate and multivariate analyses of factors predicting postoperative outcome in N0M0 cohort

Variables	Number of patients	Survival rate (%)		MST	*P*-value	Multivariate analysis	*P*-value
		3-year	5-year	(days)		Hazard ratio (95% CI)	
Tumor size, cm							
≤2	13	100.0	92.3	3011	0.014	1	
2–5	76	47.3	41.2	1059		3.47 (1.06–11.36)	0.040
>5	57	46.0	33.7	1074		3.41 (1.02–11.38)	0.046
Number of tumors							
Single	110	57.7	49.1	1504	0.001	1	
Multiple	36	29.6	17.8	715		1.86 (1.16–2.97)	0.010
Vascular invasion							
Absent	57	65.1	57.0	2761	0.007	1	
Present	89	42.9	34.0	790		1.59 (1.01–2.51)	0.045
Serosal invasion							
Absent	85	57.3	49.2	1504	0.090		
Present	61	44.0	34.7	971			
Periductal invasion							
Absent	84	54.4	44.7	1409	0.433		
Present	62	48.0	41.0	1021			

CI confidence interval, *MST* median survival time

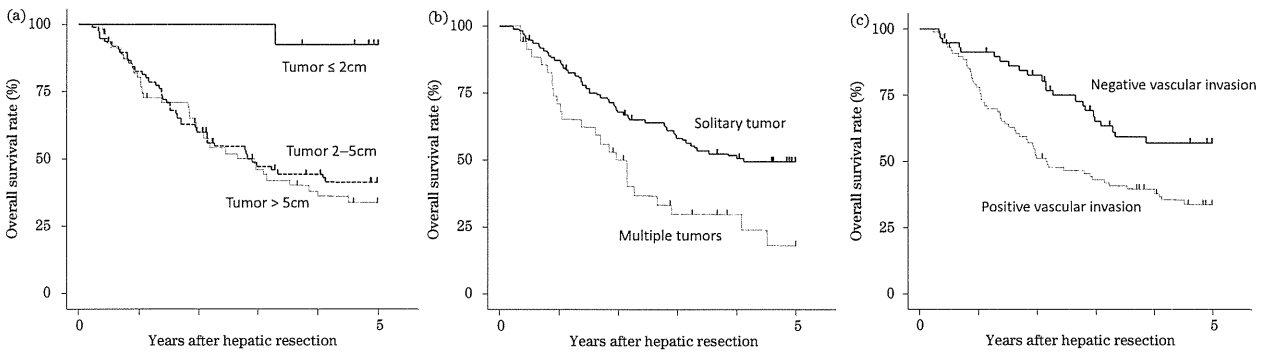

Fig. 1 The overall survival for patients in curative-resection-N0M0 cohort stratified according to tumor size (**a**), the number of tumors (**b**), and vascular invasion (**c**)

highest hazard ratio for death in the multivariate analysis. Therefore, tumor size, tumor numbers, and vascular invasion were used to determine the T classification in our proposed system. According to the univariate and multivariate analyses of the N0M0 cohort, serosal invasion did not influence survival in patients who underwent curative resection for MF-ICC. Therefore, we propose a new T classification that excludes serosal invasion.

The prognostic utility of each T classification system was assessed (Table 2). The survival curves according to the AJCC/UICC T classification failed to stratify the patients with respect to postoperative survival because the survival curves of patients with T2, T3, and T4 tumors were similar (Fig. 3a). On the contrary, the survival curves according to the LCSGJ T classification seemed to be well stratified (Fig. 3b). However, a significant difference in survival was only demonstrated between the T3 and T4 categories. After eliminating serosal invasion, 11 of the 80 patients who were classified as T3 according to the LCSGJ system were classified as T2 according to the proposed system; these patients had serosal invasion but not vascular invasion. The proposed T classification provided a better survival contrast between the T2 and T3 categories (Fig. 3c).

Survival analysis in the entire cohort and survival stratification by TNM stage

Next, univariate and multivariate analyses of prognostic factors of overall survival were performed on 233 patients who underwent curative resection for MF-ICC (Table 3). At

Table 2 Survival stratification according to T classification in N0M0 cohort

Factors	Number of patients	Survival rate (%)		Median survival days	*P*-value
		3-year	5-year		
AJCC/UICC					
T1	22	72.0	67.2	2761	0.178
T2	27	47.4	37.9	1059	0.045[a]
T3	35	48.5	34.7	1074	0.776[b]
T4	62	48.0	41.0	1021	0.893[c]
LCSGJ					
T1	8	100.0	87.5	2761	0.002
T2	28	67.3	63.6	2468	0.139[a]
T3	80	48.4	38.8	1029	0.125[b]
T4	30	30.6	18.4	715	0.040[c]
Proposed system					
T1	10	100.0	90.0	3011	<0.001
T2	37	69.2	60.4	2898	0.152[a]
T3	76	43.0	35.3	826	0.035[b]
T4	23	28.7	14.3	587	0.044[c]

[a] T1 vs T2; [b] T2 vs T3; [c] T3 vs T4

AJCC American Committee on Cancer, *LCSGJ* Liver Cancer Study Group of Japan, *UICC* International Union Against Cancer

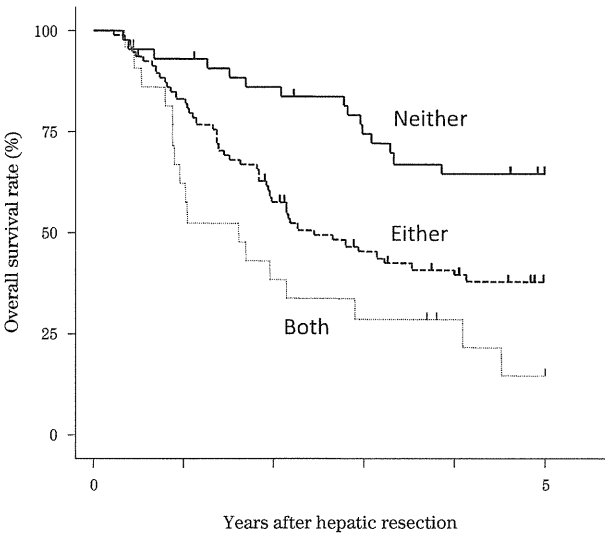

Fig. 2 The overall survival for patients in curative-resection-N0M0 cohort stratified according to the number of tumors and vascular invasion

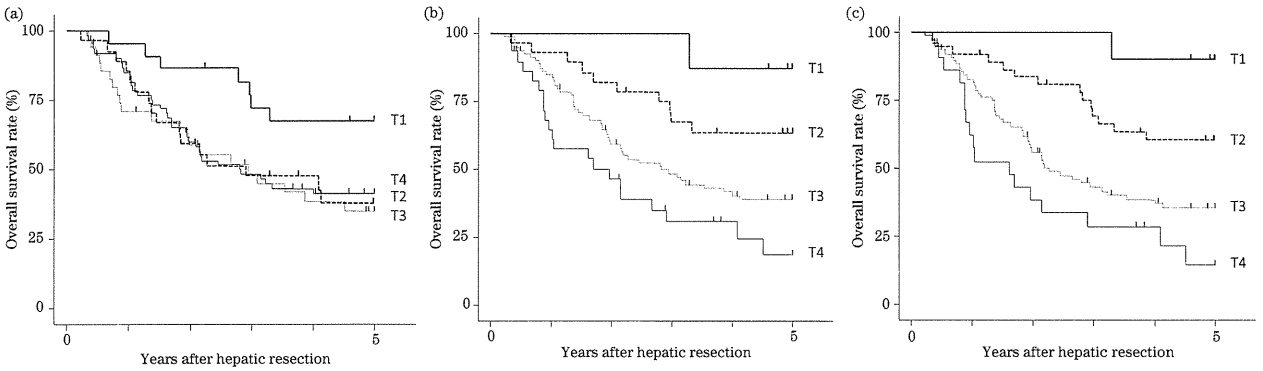

Fig. 3 The overall survival for patients in curative-resection-N0M0 cohort stratified according to T classification in American Committee on Cancer (AJCC)/International Union Against Cancer (UICC) system (**a**), Liver Cancer Study Group of Japan (LCSGJ) system (**b**), and our proposed system (**c**)

the time of analysis, the median follow-up period was 700 days (range, 67 to 4995 days). The median survival time after curative resection for MF-ICC was 715 days. The overall 3- and 5-year survival rates of the 233 patients were 39.4% and 31.1%, respectively. The univariate analysis demonstrated that tumor size, tumor number, vascular invasion, serosal invasion, and lymph node metastases were significantly associated with postoperative survival. In the multivariate analysis, ICC >2 cm, multiple tumors, and the presence of nodal metastases were independent factors associated with reduced survival duration after curative resection for MF-ICC. The 3- and 5-year overall survival rates in 87 patients with nodal metastases were 18.5% and 10.9%, respectively (Fig. 4). The postoperative outcomes in the patients with nodal metastases were dismal, even though 82 of the 87 patients underwent lymph node dissection. Among 146 patients without nodal metastases, the overall survival rates for the 74 patients who underwent lymph node dissection and for the 72 patients who underwent hepatic resection alone or lymph node sampling were 52.3% and 51.1% at 3 years and 46.6% and 39.4% at 5 years, respectively. There was no difference in survival according to lymph node dissection ($P = 0.376$).

As in the T categories, the AJCC/UICC staging system was found to poorly stratify patients with stage II tumors versus those with stage III tumors (Fig. 5a, Table 4). According to the LCSGJ staging system, significant discrimination was only observed between stage III and IVA

Table 3 Univariate and multivariate analyses of factors predicting postoperative outcome in entire cohort

Variables	Number of patients	Survival rate (%)		Median survival days	*P*-value	Multivariate analysis	*P*-value
		3-year	5-year			Hazard ratio (95% CI)	
Tumor size, cm							
≤2	16	87.5	81.3	3011	0.002	1	
2–5	124	37.1	29.6	624		3.11 (1.24–7.83)	0.016
>5	93	33.7	23.9	675		2.83 (1.09–7.34)	0.032
Number of tumors							
Single	167	46.1	37.8	1021	<0.001	1	
Multiple	66	21.4	11.0	374		1.94 (1.37–2.75)	<0.001
Vascular invasion							
Absent	65	58.5	51.5	2107	<0.001	1	
Present	168	31.8	22.9	516		1.32 (0.88–1.98)	0.183
Serosal invasion							
Absent	129	44.5	37.5	976	0.017	1	
Present	104	32.8	22.7	587		1.19 (0.86–1.65)	0.283
Periductal invasion							
Absent	109	45.0	36.5	1036	0.056		
Present	124	34.3	26.3	587			
Lymph node metastases							
Absent	146	51.7	43.2	1177	<0.001	1	
Present	87	18.5	10.9	429		2.25 (1.61–3.16)	<0.001

CI confidence interval

Table 4 Survival stratification according to tumor node metastasis (TNM) stage in entire cohort

Factors		Number of patients	Survival rate (%)		Median survival days	*P*-value
			3-year	5-year		
AJCC/UICC						
Stage	I	22	72.0	67.2	2761	<0.001
	II	27	47.4	37.9	1059	0.045[a]
	III	35	48.5	34.7	1074	0.776[b]
	IVA	149	30.8	23.3	516	0.081[c]
LCSGJ						
Stage	I	8	100.0	87.5	2761	<0.001
	II	28	67.3	63.6	2468	0.139[a]
	III	80	48.4	38.8	1029	0.125[b]
	IVA	30	30.6	18.4	715	0.040[c]
	IVB	87	18.5	10.9	740	0.120[d]
Proposed system						
Stage	I	10	100.0	90.0	3011	<0.001
	II	37	69.2	60.4	2898	0.152[a]
	III	76	43.0	35.3	826	0.035[b]
	IVA	83	23.3	14.5	486	<0.001[c]
	IVB	27	12.1	4.0	429	0.004[d]

[a] Stage I vs II; [b] Stage II vs III; [c] Stage III vs IVA; [d] Stage IVA vs IVB

AJCC American Committee on Cancer, *LCSGJ* Liver Cancer Study Group of Japan, *UICC* International Union Against Cancer

(Fig. 5b). In particular, there was no significant difference in survival between stage IVA tumors and stage IVB tumors (positive nodal metastases). Among 87 patients with nodal metastases, the overall survival rates of the 60 patients with proposed T1, T2, or T3 tumors and the 27 patients in proposed T4 tumors were 21.3% and 12.1% at 3 years and 14.0% and 4.0% at 5 years, respectively. There was a significant difference in survival between these two groups ($P = 0.008$). Moreover, the overall survival curve of the 60 patients with proposed T1, T2, or T3 tumors and nodal metastases was similar to that of the patients with T4 tumors and no nodal metastases (Fig. 6a). Therefore, patients with nodal metastases (LCSGJ stage IVB) were divided into stages IVA and IVB in the proposed staging system according to the T classification (Table 5). Of the 87 patients with nodal metastases, the 60 patients with T1, T2, or T3 tumors were classified as proposed stage IVA. The remaining 27 patients with T4 tumors were classified as stage IVB. The distributions of the patients according to the LCSGJ and proposed stages are shown in Table 6. Thus, the proposed staging system shows sequential difference in survival from stage II to IVB (Fig. 6b).

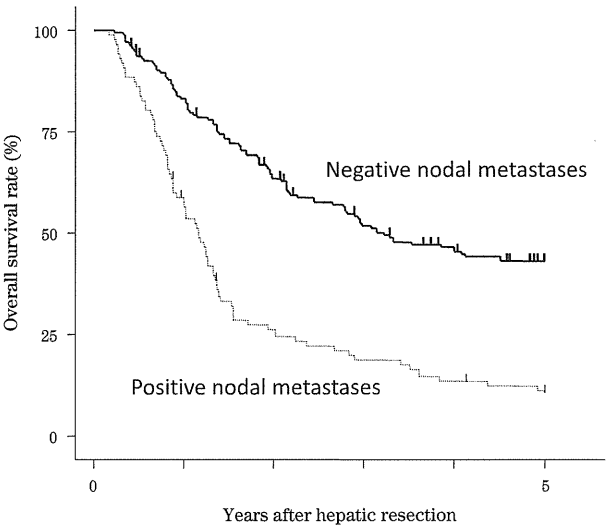

Fig. 4 The overall survival for patients in curative-resection-entire cohort stratified according to lymph node metastases

Discussion

Accurate staging systems are essential to the evaluations of treatment and clinical trial outcomes in patients with any cancers. However, since ICC is a relatively rare form, the TNM staging system for ICC had not been independent for a long time, and the staging system developed in response to clinical experiences with HCC alone had been used to treat ICC. In the 2000s, the AJCC/UICC and LCSGJ established different staging systems for ICC [20, 22]. Since then, some investigators have analyzed the accuracy of both staging systems in predicting survival after hepatic resection for

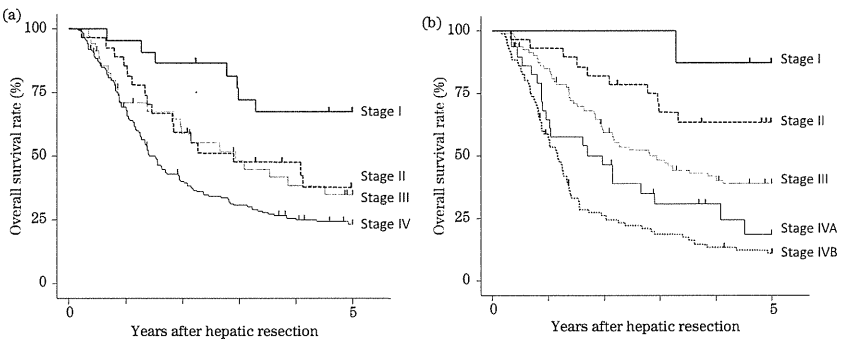

Fig. 5 The overall survival for patients in curative-resection-entire cohort stratified according to tumor node metastasis (TNM) stage in American Committee on Cancer (AJCC)/ International Union Against Cancer (UICC) system (**a**) and Liver Cancer Study Group of Japan (LCSGJ) system (**b**)

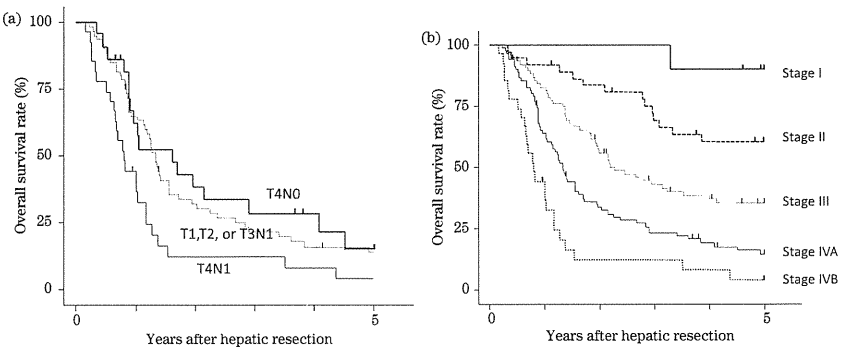

Fig. 6 The overall survival for patients with lymph node metastases in curative-resection-entire cohort stratified according to proposed T classification (**a**). The overall survival for patients in curative-resection-entire cohort stratified according to tumor node metastasis (TNM) stage in our proposed system (**b**)

Table 5 Proposed staging system for mass-forming intrahepatic cholangiocarcinoma

LCSGJ staging system		Proposed staging system
T category		
T1: meets all 3 requirements below.		T1: meets all 3 requirements below.
T2: meets any 2 requirements below.		T2: meets any 2 requirements below.
T3: meets 1 requirement below.		T3: meets 1 requirement below.
T4: meets no requirements.		T4: meets no requirements.
Requirements		
Number of tumors: Solitary		Number of tumors: Solitary
Tumor diameter: no more than 2 cm		Tumor diameter: no more than 2 cm
No vascular and serosal invasion	→	No vascular invasion
N category		
N0: no lymph nodes metastasis		N0: no lymph nodes metastasis
N1: metastasis to any lymph node		N1: metastasis to any lymph node
M category		
M0: absence of distant metastasis		M0: absence of distant metastasis
M1: presence of distant metastasis		M1: presence of distant metastasis
Stage I	T1 N0 M0	T1 N0 M0
Stage II	T2 N0 M0	T2 N0 M0
Stage III	T3 N0 M0	T3 N0 M0
Stage IVA	T4 N0 M0	T4 N0 M0
		→ T1, T2, or T3 N1 M0
Stage IVB	any T N1 M0	→ T4 N1 M0
	Any T Any N M1	Any T Any N M1

LCSGJ Liver Cancer Study Group of Japan

Table 6 Patient distribution according to the Liver Cancer Study Group of Japan (LCSGJ) and proposed staging systems

LCSG staging system	Proposed staging system					
	I	II	III	IVA	IVB	
I	8	0	0	0	0	8
II	2	26	0	0	0	28
III	0	11	69	0	0	80
IVA	0	0	7	23	0	30
IVB	0	0	0	60	27	87
	10	37	76	83	27	233

ICC and subsequently proposed some modifications [12–14, 25]. In a previous French study [14], the current AJCC/UICC stage was the only system with good accuracy in outcome prediction among various staging systems, including the LCSGJ stage. In contrast, Ribero et al. [25] reported that the AJCC/UICC system could not show a monotonicity of gradients for the T classification and stage groupings because overall survival was significantly better in the patients who were classified as T4 than in those classified as T2 (patients with multiple tumors and/or vascular invasion). In addition, in the present study, the survival curves according to the AJCC/UICC T classification were not well stratified, because the survival curves of the patients with T2, T3, and T4 tumor were similar. In the AJCC/UICC staging system, the ICC tumors with periductal invasion were classified as T4 disease. Moreover, T4 tumors were included in stage IVA, which includes any patients with nodal metastases. However, Igai et al. [12] evaluated the validity of the AJCC/UICC staging system for ICC and proposed the elimination of periductal invasion as a T category determinant. Previous studies reported that periductal invasion was not independently associated with survival after resection for ICC [6, 10–12], although a few studies reported that periductal invasion was an important predictive factor related to poor survival in patients who underwent liver resection for MF-ICC [26, 27]. The present study also recognized that periductal invasion was not a prognostic factor in the univariate and multivariate analyses. Patients with ICC tumors that perforate the visceral peritoneum (serosal invasion) are classified as having AJCC/UICC T3 disease. In the LCSGJ staging system, serosal invasion, together with vascular invasion, is a T classification component because Yamasaki [23] indicated that serosal invasion was independently associated with poor prognosis. However, in the present study, serosal invasion was not independently associated with postoperative survival, as reported in previous studies [7, 11–13]. Furthermore, when vascular invasion

was absent, no difference in survival was observed between patients with and without serosal invasion. Therefore, after eliminating serosal invasion as a component of T subgroup determination, our proposed T classification better stratified survival, which is comparable with a previous report [13].

In both the AJCC/UICC and LCSGJ systems, vascular invasion and multiple tumors are T classification components. Multiple tumors have been reported to strongly influence survival in patients who underwent hepatic resection for ICC [7–12, 21, 23]. In the present study, the postoperative outcomes in the patients with multiple tumors were extremely poor, despite the tumor distribution, and multiple tumors were an independent prognostic factor in analyses of the entire cohort and N0M0 patients. Although vascular invasion was often found to be a prognostic variable according to univariate analysis in previous studies [5–9, 11, 13], it is seldom an independent variable in multivariate analyses [5, 7, 11, 13]. In the present study, vascular invasion was also not independently associated with reduced survival in the entire cohort. However, vascular invasion was an independent predictor of poor postoperative outcomes in the N0M0 cohort, as reported in previous studies [11, 21]. Based on the multivariate analysis results, we stratified patients according to the presence of vascular invasion and tumor number. The survival curves in patients with single tumor and vascular invasion and those with multiple tumors and no vascular invasion were similar, but the overall survival rates in the patients with both factors were significantly lower than the rates in the patients with either vascular invasion or multiple tumors. These findings suggest that vascular invasion and multiple tumors synergistically increase the risk of reduced survival in patients with MF-ICC. However, in the AJCC/UICC T classification, ICC with both factors as well as ICC having either vascular invasion or multiple tumors alone is defined as T2 disease, which could be another reason why the survival curves according to the AJCC/UICC T classification were not well stratified in the present study.

Whether tumor size affects survival in patients who undergo liver resection for ICC is controversial. Nathan et al. [21] recognized that tumor size did not predict survival in patients with ICC in any analyses that used a cutoff value of 2 or 5 cm. Therefore, tumor size was omitted from the AJCC/UICC staging schema. Other investigators also reported that tumor size (using cutoff values of 5 or 3 cm) was not an independent prognostic factor [5–13]. Meanwhile, the LCSGJ staging system included tumor size, using a cutoff value of 2 cm, because tumor >2 cm was an independent prognostic factor for MF-ICC, as Yamasaki [23] reported. In the present study, patients with ICC tumors ≤2 cm also had a markedly favorable prognosis; a 5-year survival rate of 92.3% was reported in the N0M0 cohort, although no difference in survival was noted between patients with tumors of 2–5 cm and those with tumors >5 cm. Moreover, ICC tumors >2 cm had the strongest impact on postoperative survival. However, the impact of tumor size on survival could not be analyzed in the patients with multiple tumors and/or vascular invasion because only 13 (8.9%) of the 146 N0M0 patients had ICC tumors ≤2 cm. Previous studies reported that only 3% of patients had LCSGJ stage I tumors (≤2 cm single tumor without vascular invasion or nodal metastases) [14, 23], as it is difficult to detect early-stage ICC. Okabayashi et al. [6] also reported that none of the 60 patients who underwent hepatic resection for MF-ICC had tumors ≤2 cm in diameter. The real impact of tumor size on survival should be tested in a much larger population.

In the present study, the postoperative outcomes of patients with nodal metastases were extremely poor, regardless of lymph node dissection, and the presence of nodal metastases was an independent predictor of reduced survival. Lymph node metastasis is an important prognostic factor in patients who undergo hepatic resection for ICC [5–13, 21, 23]. Therefore, in the LCSGJ staging system, ICC with nodal metastases is classified into stage IVB, as is ICC with distant metastases. de Jong et al. [11] reported that the presence of multiple tumors or vascular invasion, either alone or together, could not stratify patients with nodal metastases with regard to postoperative survival, but the present study demonstrated that the survival rate of patients with T4 tumors was significantly lower than that of other patients when nodal metastases were present. Therefore, we propose that patients with nodal metastases should be divided into stage IVA or IVB, according to T classification, due to the improved survival stratification.

In conclusion, the AJCC/UICC staging system failed to stratify the Japanese patients with MF-ICC. We propose some modifications to the LCSGJ staging system for MF-ICC. Thus, the proposed staging system could better stratify patients with regard to survival after hepatic resection for MF-ICC. However, like the LCSGJ staging system, a weakness of this system is due to the assumption of equal power for tumor size, tumor number, and vascular invasion. In particular, the real impact of tumor size on survival is uncertain. Further studies should be conducted on much larger populations.

Conflict of interest None declared.

References

1. Ikai I, Arii S, Okazaki M, Okita K, Omata M, Kojiro M, et al. Report of the 17th Nationwide Follow-up Survey of Primary Liver Cancer in Japan. Hepatol Res. 2007;37:676–91.
2. Khan SA, Thomas HC, Davidson BR, Taylor-Robinson SD. Cholangiocarcinoma. Lancet. 2005;366:1303–14.

3. Okuda K, Nakanuma Y, Miyazaki M. Cholangiocarcinoma: recent progress. Part 1: epidemiology and etiology. J Gastroenterol Hepatol. 2002;17:1049–55.
4. Khan SA, Taylor-Robinson SD, Toledano MB, Beck A, Elliott P, Thomas HC. Changing international trends in mortality rates for liver, biliary and pancreatic tumours. J Hepatol. 2002;37:806–13.
5. Uenishi T, Kubo S, Yamazaki O, Yamada T, Sasaki Y, Nagano H, et al. Indications for surgical treatment of intrahepatic cholangiocarcinoma with lymph node metastases. J Hepatobiliary Pancreat Surg. 2008;15:417–22.
6. Okabayashi T, Yamamoto J, Kosuge T, Shimada K, Yamasaki S, Takayama T, et al. A new staging system for mass-forming intrahepatic cholangiocarcinoma: analysis of preoperative and postoperative variables. Cancer. 2001;92:2374–83.
7. Choi SB, Kim KS, Choi JY, Park SW, Choi JS, Lee WJ, et al. The prognosis and survival outcome of intrahepatic cholangiocarcinoma following surgical resection: association of lymph node metastasis and lymph node dissection with survival. Ann Surg Oncol. 2009;16:3048–56.
8. Ribero D, Pinna AD, Guglielmi A, Ponti A, Nuzzo G, Giulini SM, et al. Surgical approach for long-term survival of patients with intrahepatic cholangiocarcinoma: a multi-institutional analysis of 434 patients. Arch Surg. 2012;147:1107–13.
9. Yedibela S, Demir R, Zhang W, Meyer T, Hohenberger W, Schönleben F. Surgical treatment of mass-forming intrahepatic cholangiocarcinoma: an 11-year Western single-center experience in 107 patients. Ann Surg Oncol. 2009;16:404–12.
10. Uchiyama K, Yamamoto M, Yamaue H, Ariizumi S, Aoki T, Kokudo N, et al. Impact of nodal involvement on surgical outcomes of intrahepatic cholangiocarcinoma: a multicenter analysis by the Study Group for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. J Hepatobiliary Pancreat Sci. 2011;18:443–52.
11. de Jong MC, Nathan H, Sotiropoulos GC, Paul A, Alexandrescu S, Marques H, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. J Clin Oncol. 2011;29:3140–5.
12. Igami T, Ebata T, Yokoyama Y, Sugawara G, Takahashi Y, et al. Staging of peripheral-type intrahepatic cholangiocarcinoma: appraisal of the new TNM classification and its modifications. World J Surg. 2011;35:2501–9.
13. Uenishi T, Yamazaki O, Yamamoto T, Hirohashi K, Tanaka H, Tanaka S, et al. Serosal invasion in TNM staging of mass-forming intrahepatic cholangiocarcinoma. J Hepatobiliary Pancreat Surg. 2005;12:479–83.
14. Farges O, Fuks D, Le Treut YP, Azoulay D, Laurent A, Bachellier P, et al. AJCC 7th edition of TNM staging accurately discriminates outcomes of patients with resectable intrahepatic cholangiocarcinoma: by the AFC-IHCC-2009 study group. Cancer. 2011; 117:2170–7.
15. Saiura A, Yamamoto J, Kokudo N, Koga R, Seki M, Hiki N, et al. Intrahepatic cholangiocarcinoma: analysis of 44 consecutive resected cases including 5 cases with repeat resections. Am J Surg. 2011;201:203–8.
16. Inoue K, Makuuchi M, Takayama T, Torzilli G, Yamamoto J, Shimada K, et al. Long-term survival and prognostic factors in the surgical treatment of mass-forming type cholangiocarcinoma. Surgery. 2000;127:498–505.
17. Nakagohri T, Kinoshita T, Konishi M, Takahashi S, Gotohda N. Surgical outcome and prognostic factors in intrahepatic cholangiocarcinoma. World J Surg. 2008;32:2675–80.
18. Murakami Y, Uemura K, Sudo T, Hayashidani Y, Hashimoto Y, Nakamura H, et al. Adjuvant gemcitabine plus S-1 chemotherapy improves survival after aggressive surgical resection for advanced biliary carcinoma. Ann Surg. 2009;250:950–6.
19. Gürlevik E, Fleischmann-Mundt B, Armbrecht N, Longerich T, Woller N, Kloos A, et al. Adjuvant gemcitabine therapy improves survival in a locally induced, r0-resectable model of metastatic intrahepatic cholangiocarcinoma. Hepatology. 2013;58:1034–41.
20. Edge SB, editor. Intrahepatic bile ducts. AJCC cancer staging manual, 7th edn. New York: Springer; 2009.
21. Nathan H, Aloia TA, Vauthey JN, Abdalla EK, Zhu AX, Schulick RD, et al. A proposed staging system for intrahepatic cholangiocarcinoma. Ann Surg Oncol. 2009;16:14–22.
22. The Liver Cancer Study Group of Japan. General rules for the clinical and pathological study of primary liver cancer, Second edn. Tokyo: Kanehara; 2003.
23. Yamasaki S. Intrahepatic cholangiocarcinoma: macroscopic type and stage classification. J Hepatobiliary Pancreat Surg. 2003;10: 288–91.
24. Terminology Committee of the IHPBA: terminology of liver anatomy and resections. HPB. 2000;2:333–9.
25. Ribero D, Nuzzo G, Amisano M, Tomatis M, Guglielmi A, Giulini SM, et al. Comparison of the prognostic accuracy of the sixth and seventh editions of the TNM classification for intrahepatic cholangiocarcinoma. HPB (Oxford). 2011;13:198–205.
26. Guglielmi A, Ruzzenente A, Campagnaro T, Pachera S, Valdegamberi A, Nicoli P, et al. Intrahepatic cholangiocarcinoma: prognostic factors after surgical resection. World J Surg. 2009;33: 1247–54.
27. Shimada K, Sano T, Sakamoto Y, Esaki M, Kosuge T, Ojima H. Surgical outcomes of the mass-forming plus periductal infiltrating types of intrahepatic cholangiocarcinoma: a comparative study with the typical mass-forming type of intrahepatic cholangiocarcinoma. World J Surg. 2007;31:2016–22.

The American Journal of Surgery (2014) ■, ■-■

The American Journal of Surgery®

Preoperative cholangitis during biliary drainage increases the incidence of postoperative severe complications after pancreaticoduodenectomy

Yuji Kitahata, M.D., Manabu Kawai, M.D., Ph.D., Masaji Tani, M.D., Ph.D., Seiko Hirono, M.D., Ph.D., Ken-ichi Okada, M.D., Ph.D., Motoki Miyazawa, M.D., Ph.D., Atsushi Shimizu, M.D., Ph.D., Hiroki Yamaue, M.D., Ph.D.*

Second Department of Surgery, Wakayama Medical University School of Medicine, 811-1 Kimiidera, Wakayama 641-8510, Japan

KEYWORDS:
Cholangitis;
Biliary drainage;
Pancreaticoduodenectomy;
Postoperative complications;
Delayed gastric emptying;
Wound infection

Abstract

BACKGROUND: It remains controversial how preoperative biliary drainage affects occurrence of severe complications after pancreaticoduodenectomy (PD).

METHODS: One hundred twenty-seven patients (60 external drainage and 67 internal drainage) required biliary drainage before PD were retrospectively reviewed.

RESULTS: Preoperative cholangitis in internal drainage group (22.4%) occurred significantly more often than in external drainage group (1.7%; $P < .001$). The incidence of severe complications (grade III or more) was significantly higher in patients with cholangitis (62.5%) than in those without it (25.2%; $P = .002$). The incidence of delayed gastric emptying was significantly higher in patients with cholangitis (31.2%) than in those without it (5.4%; $P = .001$). A multivariate logistic regression analysis revealed that preoperative cholangitis (odds ratio 4.61, 95% confidence interval 1.3 to 16.5; $P = .019$) was the independent risk factor for severe complications after PD.

CONCLUSIONS: Preoperative cholangitis during biliary drainage significantly increases incidence of severe complications after PD.

Previous retrospective studies have reported benefits of preoperative biliary drainage.[1,2] In contrast, some retrospective studies have reported that preoperative biliary drainage increased the risk for morbidity or mortality.[3–5] A recent randomized controlled trial reported that routine preoperative biliary drainage for patients with pancreaticoduodenectomy (PD) increased the incidence of all complications including cholangitis, stent dysfunction, and the need for repeated stent exchange.[6] One of the major problems is that preoperative biliary drainage may lead to biliary drainage–related complications such as cholangitis, pancreatitis, hemorrhage, or perforation. Moreover, biliary drainage–related complications may introduce postoperative complications. However, it remains unclear what factors in preoperative biliary drainage affect the occurrence of postoperative complications after PD. Moreover, biliary

The authors declare no conflicts of interest.

* Corresponding author. Tel.: +81-73-441-0613; fax: +81-73-446-6566.

E-mail address: yamaue-h@wakayama-med.ac.jp

Manuscript received July 22, 2013; revised manuscript August 30, 2013

0002-9610/$ - see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.amjsurg.2013.10.021

drainage–related complications may introduce postoperative complications.

Obstructive jaundice may be related to hepatic dysfunction, disturbances in coagulation, and the development of cholangitis. Kimmings et al[1] reported that preoperative biliary decompression improves nutritional metabolic and immune function and reduces postoperative complications after PD. Therefore, preoperative biliary drainage may still be required to improve obstructive jaundice, when patients who plan to receive neoadjuvant chemotherapy or chemoradiation therapy have this condition. Therefore, it is important to evaluate how to manage biliary drainage. Another issue in preoperative biliary drainage is which approach to use, internal or external drainage. However, it remains controversial which is the most appropriate approach for preoperative biliary drainage.[7]

The aim of this study was to clarify how biliary drainage–related complications affect postoperative complications after PD and to evaluate the appropriate approach for preoperative biliary drainage after PD by comparing internal and external biliary drainage.

Methods

Patients

Between April 2005 and December 2010, 292 patients underwent PD for periampullary tumors and pancreatic tumors at Wakayama Medical University Hospital. Of these, 127 patients with PD had preoperative biliary drainage for obstructive jaundice or hepatic dysfunction (transaminase >100 IU/mL). We retrospectively reviewed a prospectively maintained database to assess patient demographics, type of preoperative biliary drainage, operative details, perioperative complications, and pathology in the 127 patients with preoperative biliary drainage.

Type of preoperative biliary drainage

A jaundiced patient was defined as patients with symptoms such as cholangitis, serum bilirubin level greater than 5.0 mg/dL, or hepatic dysfunction (transaminase > 100 IU/mL) for tumor-causing obstructive jaundice. When gastroenterologist or surgeon diagnosed the jaundiced patients who required PD, the patients underwent preoperative biliary drainage by percutaneous transhepatic biliary drainage (PTBD), endoscopic nasobiliary drainage (ENBD), or endoscopic retrograde biliary drainage (ERBD) in Japan. Approach for biliary drainage was chosen by the gastroenterologist or surgeon. Because Japanese guideline for preoperative biliary drainage proposed that a method for preoperative biliary drainage should be used that can be safely performed with the equipment and techniques available at each facility for clinical question concerning to appropriate procedures for preoperative biliary drainage.[8] PTBD and ENBD were performed as the types of external drainage, and ERBD was performed as the internal drainage. Plastic stents were used for ERBD. PTBD and ENBD were performed as the types of external drainage, and ERBD was performed as the internal drainage. In the procedure of PTBD, the intrahepatic bile duct was punctured using a hollow needle under ultrasound guidance. A guidewire was inserted into the elastic needle after backflow of bile was confirmed. A 7-French PTBD tube was then passed over the guidewire. The procedure of ENBD was performed using endoscopic retrograde cholangiopancreatography (ERCP) with a conventional side-viewing duodenoscope in a standard manner. A guidewire was passed through the catheter into the bile duct, after an endoscopic catheter was cannulated into the bile duct. The catheter is withdrawn, and a 7-French ENBD tube is passed along the guidewire. The endoscope is then removed while applying pushing pressure on the ENBD tube to keep it in place. Afterward, the tube that exits orally was pulled back out nasally. The procedure of ERBD was performed using ERCP. "Pigtail-type" plastic stent was used as ERBD tube.

Jaundiced patients were given 2 g cefazolin intravenously 30 minutes before biliary drainage. When cholangitis occurred during biliary drainage, levofloxacin, 500 mg/d, was intravenously administrated until fever came down. An additional drainage was performed or a new stent exchange was performed if signs of inadequate bile drainage developed, whether cholangitis or not.

Surgical procedure

All patients underwent PD, pylorus-preserving pancreaticoduodenectomy (PpPD), or pylorus-resecting pancreaticoduodenectomy (PrPD).[9] In PD, 30% to 40% distal gastrectomy was performed. On the other hand, in PrPD, the stomach is divided just adjacent the pylorus ring. Therefore, the nearly total stomach more than 95% was preserved, although the pylorus ring was resected in PrPD. In PpPD, the proximal duodenum was divided 3 to 4 cm distal to the pylorus ring; 20-mm occluding atraumatic bulldog clamp was positioned across the transected common hepatic duct to minimize intraperitoneal contamination of bile until the start of an end-to-side hepaticojejunostomy. All patients underwent PD with the reconstruction, and pancreaticojejunostomy after PD, PpPD, and PrPD were performed by duct-to-mucosa, end-to-side pancreaticojejunostomy in all patients. A 5-Fr polyethylene pancreatic duct drainage tube (Sumitomo Bakelite Co., Tokyo, Japan) was usually used as a stent for pancreaticojejunostomy in all patients except those with a dilated duct size greater than 5 mm. Then an end-to-side hepaticojejunostomy was performed by 1-layer anastomosis (5-0PDS-II) 10 to 15 cm distal to the pancreaticojejunostomy. No stent was used for the biliary anastomosis. Duodenojejunostomy in PpPD or gastrojejunostomy in PD or PrPD was performed by 2-layer anastomosis (4-0PDS-II

Table 1 Demographics of 127 patients with preoperative biliary drainage

	Number of patients (%)
Indication for biliary drainage	
Obstructive jaundice	120 (94.4)
Hepatic dysfunction (transaminase > 100 IU/mL)	7 (5.6)
Type of preoperative biliary drainage	
PTBD	50 (39.3)
ENBD	10 (7.9)
ERBD	67 (52.8)
Internal/external drainage*	60 (47.2)/67 (52.8)
Preoperative biliary instrumentation	
ERCP with biliary drainage	77 (60.6)
Primary PTBD	43 (33.8)
PTBD after failed ERCP	7 (5.6)
Number of procedures per patient	
1 procedure	110 (86.6)
2 procedures	17 (13.4)
Biliary drainage-related complications	18 (14.1)
Cholangitis	16 (12.6)
Cholangitis because of stent occlusion	10 (7.8)
Pancreatitis	2 (1.6)

ENBD = endoscopic nasobiliary drainage; ERBD = endoscopic retrograde biliary drainage; PTBD = percutaneous transhepatic biliary drainage.
*Internal drainage was defined as ERBD. External drainage was defined as PTBD or ERBD.

and 3-0 silk) via an antecolic route.[10] One drain was routinely placed anterior to the pancreaticojejunostomy.

Postoperative management

Flomoxef (1 g) as prophylactic antibiotics was administrated before skin incision. Afterward, antibiotics were administrated every 3 hours during the operative procedure. The duration for prophylactic antibiotics was 2 days postoperatively in accordance with the guideline of the Japan Society of Surgical Infection. A nasogastric tube was inserted before surgery and removed from all patients on postoperative day 1. Oral intake was routinely started 3 or 4 days after surgery. If bile leakage and bacterial contamination were absent, this drain was removed on postoperative day 4 in all enrolled patients.[11] All patients received an intravenous H2 blocker (famotidine; Astellas Pharma, Inc., Tokyo, Japan) for 2 weeks postoperatively. Prophylactic octreotide or prokinetic agents, such as erythromycin, were not administered postoperatively. Adjuvant chemotherapy was provided to patients with periampullary carcinoma or pancreatic carcinoma by the regimen in accordance with our protocol based on gemcitabine, S-1, or the others, unless contraindicated by a patient's condition.

Preoperative and postoperative complications

Preoperative cholangitis was defined by the new diagnostic criteria of acute cholecystitis referred to as the Tokyo Guidelines 2013.[12] Acute pancreatitis is defined as follows: abdominal pain and a serum concentration of pancreatic enzymes (amylase or lipase) 2 or more times the upper limit of normal that required more than 1 night of hospitalization. Stent occlusion is diagnosed in the case of recurring obstructive jaundice with necessary stent replacement.

Infectious complications were defined as any complication with evidence of associated localized or systemic infection indicated by fever and leukocytosis and confirmed by imaging and/or positive culture. Moreover, any positive cultures, such as positive wound cultures, drain cultures, or blood cultures, required drainage or administration of antibiotics different from those received at the time of surgery. The diagnosis of pancreatic fistula was determined by the International Study Group on Pancreatic Fistula guideline.[13] Delayed gastric emptying (DGE) was defined according to a consensus definition and clinical grading of postoperative DGE proposed by the International Study Group of Pancreatic Surgery (ISGPS).[14] DGE was then classified into 3 categories (grade A, B, or C) by the ISGPS clinical criteria based on the clinical course and postoperative management. Postoperative complications, such as intra-abdominal abscess, intra-abdominal hemorrhage, bile leakage, wound infection, and sepsis in this study, were classified based on the Clavien classification.[15] Severe complications were defined in this study as a condition that was grade III or more based on the Clavien classification. Mortality was defined as death within 30 days after surgery.

Statistical analysis

Data are expressed as mean ± SD or median (range). Patient characteristics and perioperative and postoperative

factors between 2 groups were compared using chi-square statistics, Fisher exact test, and Mann–Whitney *U* test. Variables with *P* less than .1 were entered into a logistic regression model to determine the independent risk factors of postoperative complications. The independent risk factors of the variables were expressed as odds ratios with their 95% confidence intervals. Statistical significance was defined as *P* less than .05. All statistical analyses were performed with SPSS software, version 20 (SPSS, Chicago, IL).

Results

Patient characteristics

Table 1 shows demographics of 127 patients with preoperative biliary drainage. In the 127 patients with preoperative biliary drainage, external drainage was performed in 60 patients (PTBD in 50 cases and ENBD in 10 cases) and internal drainage (ERBD) was performed in 67 patients. Drainage was successfully established in all patients who underwent preoperative biliary drainage, although 17 patients (13.4%) had 2 procedures of biliary drainage for PTBD after failed ERCP or plastic stent occlusion. Biliary drainage–related complications occurred in 18 patients (14.1%). Cholangitis occurred in 16 patients (12.6%). In 10 of 16 patients (7.8%) with cholangitis, stent occlusion resulting in stent replacement occurred. There was no biliary drainage–related death.

Table 2 compares the patient characteristics, preoperative status, and perioperative status between the external drainage and internal drainage groups. Total bilirubin before biliary drainage between the 2 groups was similar (8.3 ± 5.7 mg/dL in external drainage group vs 7.5 ± 5.8 mg/dL in internal drainage group). Moreover, there was no significant difference in the waiting periods for operation from drainage between the 2 groups (20 ± 11 days in external drainage group vs 28 ± 15 days in internal drainage group). Regarding operative factors, median intraoperative bleeding (745 mL in external drainage group vs 550 mL in internal drainage group; $P = .012$) and the rate of transfusion (47% in external drainage group vs 19% in internal drainage group; $P = .001$) were significantly greater in the external drainage group.

Preoperative and postoperative complications between external drainage and internal drainage

Table 3 compares preoperative and postoperative complications between the external drainage and internal drainage groups. Preoperative cholangitis occurred with significantly greater frequency in the internal drainage group (1.7% in external drainage group vs 22.4% in internal drainage group; $P < .001$). In this study, no incidence of hemorrhage and perforation because of biliary drainage occurred in either group.

Table 2 Patient characteristics according to types of preoperative biliary drainage

	External drainage (n = 60)	Internal drainage (n = 67)	*P* value
Age	70 ± 9	68 ± 8	.333
Gender (male/female)	32/28	39/28	.581
Total bilirubin before biliary drainage (mg/dL)*	8.3 ± 5.7	7.5 ± 5.8	.842
Operative procedure (PD/PpPD/PrPD)	8/48/4	2/43/22	.0001
Histology (pancreatic cancer/other)	26/34	29/38	.995
Pancreatic adenocarcinoma	26	29	
Bile duct carcinoma	24	25	
Ampullary adenocarcinoma	5	7	
Duodenal adenocarcinoma	0	1	
Intraductal papillary neoplasms	2	0	
Pancreatic endocrine tumor	1	1	
Tumor-forming pancreatitis	3	3	
Neoadjuvant therapy (yes/no)	0/60	3/64	.144
Operative time (min)			
Median (range)	359 (259–723)	370 (219–584)	.475
Intraoperative bleeding (mL)			
Median (range)	745 (45–6,320)	550 (80–7,335)	.012
Red blood cell transfusion (yes/no)	28/32	13/54	.001
Pancreatic texture (soft/hard)	31/29	35/32	.949
Waiting periods for operation from drainage (d)			
Median (range)	19 (5–74)	26 (5–79)	.066
Postoperative hospital stay (d)			
Median (range)	24 (5–113)	19 (8–223)	.199

PD = pancreaticoduodenectomy; PpPD = pylorus-preserving pancreaticoduodenectomy; PrPD = pylorus-resecting pancreaticoduodenectomy.
*Normal range of total bilirubin level: .2–1.2 mg/dL.