Table 2 Baseline hematological values and laboratory data

Variables	T2	T3	T4	*P*
WBC (/μl)	5,950 (3,500–12,000)	6,100 (1,300–9,800)	6,100 (2,200–13,200)	0.742
Neu (/μl)	3,955 (1,760–9,350)	3,990 (530–7,720)	4,280 (1,190–10,790)	0.361
Lym (/μl)	1,585 (720–2,990)	1,380 (480–3,250)	1,410 (620–2,510)	0.032
Mono (/μl)	295 (100–550)	290 (60–800)	270 (110–620)	0.202
Hb (g/dl)	13.65 (6.7–16.5)	12.8 (5.5–16.5)	12.3 (6.0–16.3)	<0.001
Plt ($\times 10^4$/μl)	24.45 (9.7–41.4)	27.3 (8.0–51.2)	26.4 (15.3–56.5)	0.146
NLR	2.568 (0.863–5.927)	2.788 (0.898–13.542)	3.322 (1.311–9.695)	0.004
CRP (mg/dl)	0.1 (0–6.1)	0.1 (0–5.7)	0.1 (0–10.4)	0.017
Alb (g/dl)	4.2 (3.2–4.8)	4.1 (2.6–4.7)	4.0 (2.7–4.6)	0.063
PT (s)	11.4 (10.5–12.7)	11.5 (10.0–13.0)	11.4 (10.4–12.8)	0.07
APTT (s)	26.8 (21–38)	26.3 (21.0–40.0)	28.1 (21.0–43.0)	0.067
CEA (ng/ml)	2.9 (0.6–32.8)	2.9 (0.6–187)	2.1 (0.6–155.2)	0.029
CA19-9 (U/ml)	12 (1–139)	12.5 (0.1–412)	14.0 (0.1–633)	0.354

Values are median (range). Data for each T stage are shown. The significance was evaluated using the Kruskal–Wallis test

Neu neutrophil count, *Lym* lymphocyte count, *Mono* monocyte count, *NLR* neutrophil/lymphocyte ratio

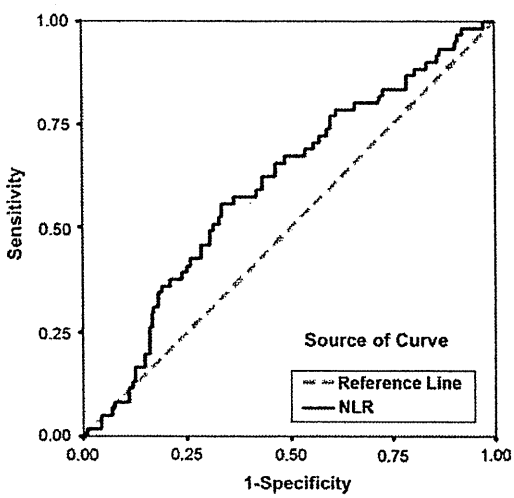


Fig. 1 ROC curve to assess the predictive value of the NLR in determining the T4 stage is shown

Discussion

Blood samples were easily assessable and reliable factors for preoperative prediction. In particular, NLR has been reported to be a prognostic factor in gastric cancer patients [15, 17, 20–22]. We analyzed the relationship between NLR and tumor-related factors in patients with wall-penetrating gastric cancer, for whom we sometimes need to consider neoadjuvant therapies. A large phase III trial demonstrated the efficacy of neoadjuvant chemotherapy in similar patients who were estimated to be stage II or higher with neither distant metastases nor locally advanced inoperable disease [5]. In the present study, NLR was correlated with T stage rather than with the nodal status or the histological features. The result suggested that the tissue damage and remodeling around invasive tumors had an effect on the systemic inflammatory response. The prognostic value of NLR in gastric cancer might depend on the T stage.

Neutrophils represent early acute inflammation and migrate to the affected sites to neutralize and eliminate potentially injurious stimuli [24]. Increased neutrophil counts have been observed in patients with gastric cancer [25]. Likewise, the production of tumor-promoting inflammatory chemokines and cytokines has been shown to trigger the recruitment of myeloid cells to most tumors related to inflammation, and gastric cancer cells overexpress C-X-C motif chemokine ligand 8 (CXCL8, known as IL-8), which induces migration of the chemokine receptor CXCR1 (also known as IL-8 receptor α) expressed on neutrophils across the tumor site [25]. Recruited neutrophils, along with the tumor-associated macrophages (TAM), have been shown to be a major source of matrix metalloproteinase 9 (MMP9) in various murine tumor models [26]. The prior partial degradation of the extracellular matrix by MMPs allows cell infiltration into the tissue [27]; in addition, vascular endothelial growth factor A (VEGF-A), derived from TAM, mediates endothelial cell mitogenesis and vascular permeability [28]. The present study demonstrated a T-stage-dependent increase in the neutrophil count in the peripheral blood (Table 2), reflecting recruitment of neutrophils from the bone marrow to the tumor site; however, no statistically significant differences were observed.

The lymphocytopenia was presumably a part of an immune-tolerated microenvironment around the tumor and has been suggested as an independent prognostic factor in

Table 3 Univariate and multivariate logistic regression analyses to determine the risk of stage T4

Variables	*n*	Univariate analysis		Multivariate analysis		
		OR (95% CI)	*P*	OR (95% CI)	*B*	*P*
Lym <1,000 (/μl)	41	1.673 (0.805–3.477)	0.168	–	–	–
Hb <13.0 (g/dl)	121	2.020 (1.126–3.624)	0.018	1.875 (1.005–3.500)	0.639	0.048
Plt >25.0 ($\times 10^4$/μl)	142	1.291 (0.722–2.306)	0.389	–	–	–
CRP >1 (mg/dl)	20	2.377 (0.924–6.117)	0.072	–	–	–
NLR >3.2	103	2.036 (1.139–3.639)	0.016	2.206 (1.187–4.100)	0.783	0.012
Alb <3.5 (g/dl)	24	2.146 (0.889–5.183)	0.090	–	–	–
PT >median	99	0.777 (0.403–1.403)	0.403	–	–	–
APTT >median	133	1.846 (0.990–3.442)	0.054	–	–	–
CEA >5 (ng/ml)	47	0.826 (0.384–1.773)	0.623	–	–	–
CA19-9 >37 (U/ml)	35	2.175 (1.020–4.640)	0.044	2.073 (0.918–4.679)	0.718	0.079
Poorly differentiated	143	3.061 (1.602–5.848)	0.001	3.134 (1.593–6.167)	1.144	0.001

The significance in univariate analysis was evaluated using χ^2 and Fisher's exact tests. The significance in multivariate analysis was evaluated using multiple logistic regression analysis. The regression coefficient *B* is also given

several cancers [18]. Interestingly, a significant decrease in the lymphocyte count was also observed in a T-stage-dependent manner (Table 2). This result indicated the possibility that neutrophil-induced tissue damage and remodeling around the tumor site contributed to the establishment of the host's adaptive immunity.

T4 disease has newly been defined in the 7th edition of the UICC TNM classification as a tumor perforating the serosa or invading adjacent structures [23], and includes remodeling through all the gastric layers. In cases with T4 disease, the neutrophil counts reached their peak, while the lymphocyte counts reached their nadir, yielding the maximum NLR (Table 2). An earlier study also reported a consistent T-stage-dependent increase in NLR in gastric cancer [20]. Furthermore, a high NLR, defined as >3.2 in the present study, was an independent predictor of T4 disease according to multiple logistic regression analysis, as was a decrease in the Hb and poorly differentiated tumor histology. Anemia presumably reflected the blood loss at the tumor site. CA19-9 was correlated with the T stage but was not an independent predictive factor for T4 disease. The histological differentiation grade was the most reliable risk factor, but the histology of biopsy samples obtained through endoscopic examination did not always match that of the corresponding resected specimens. Although serum CRP and Alb have been previously suggested as inflammation-based prognostic factors in advanced cancers [16, 29, 30], both were not meaningful predictive factors for T4 disease. Therefore, the high baseline of NLR was suggested as a valuable predictive factor for T4 disease, and its predictive value was superior to serum tumor markers.

The clinical diagnostic accuracy rate for T4 disease was 50.3% in the present study. This low accuracy rate was attributable to the conventional axial CT images without gastric water filling or radiological examinations. Actually, it was known that the clinical TNM staging of gastric cancer before treatment was not in accord with pathological staging in a substantial number of cases. Recently, the accuracy of preoperative staging of gastric cancer was improved by MDCT with multiplanar reconstruction (MPR) images. The diagnostic accuracy of MDCT for T4 disease was reported to be up to 93% [8–11], and a prospective study to confirm the reproducibility in a larger sample is awaited. Though the NLR seems to add valuable preoperative information to clinical TNM staging, the utility of NLR still requires the comparison with novel imaging modalities like MDCT before the introduction into clinical practice.

In conclusion, we found NLR as an independent predictive factor for T4 disease to be superior to other serum factors. The clinical utility of NLR still needs to be confirmed with prospective analysis.

Disclosure The authors have no conflicts of interest or financial ties to disclose.

References

1. Jemal A, Siegel R, Ward E et al (2009) Cancer statistics, 2009. CA Cancer J Clin 59:225–249
2. Noguchi Y, Yoshikawa T, Tsuburaya A et al (2000) Is gastric carcinoma different between Japan and the United States? Cancer 89:2237–2246
3. Maruyama K, Okabayashi K, Kinoshita T (1987) Progress in gastric cancer surgery in Japan and its limits of radicality. World J Surg 11:418–425. doi:10.1007/BF01655804
4. Sakuramoto S, Sasako M, Yamaguchi T et al (2007) Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 357:1810–1820

5. Cunningham D, Allum WH, Stenning SP et al (2006) Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 355:11–20
6. Macdonald JS, Smalley SR, Benedetti J et al (2001) Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 345:725–730
7. Brennan MF (2005) Current status of surgery for gastric cancer: a review. Gastric Cancer 8:64–70
8. Chen CY, Hsu JS, Wu DC et al (2007) Gastric cancer: preoperative local staging with 3D multi-detector row CT—correlation with surgical and histopathologic results. Radiology 242:472–482
9. Habermann CR, Weiss F, Riecken R et al (2004) Preoperative staging of gastric adenocarcinoma: comparison of helical CT and endoscopic US. Radiology 230:465–471
10. Hwang SW, Lee DH, Lee SH et al (2010) Preoperative staging of gastric cancer by endoscopic ultrasonography and multidetector-row computed tomography. J Gastroenterol Hepatol 25:512–518
11. Kumano S, Murakami T, Kim T et al (2005) T staging of gastric cancer: role of multi-detector row CT. Radiology 237:961–966
12. de Graaf GW, Ayantunde AA, Parsons SL et al (2007) The role of staging laparoscopy in oesophagogastric cancers. Eur J Surg Oncol 33:988–992
13. Coussens LM, Werb Z (2002) Inflammation and cancer. Nature 420:860–867
14. Mantovani A, Allavena P, Sica A et al (2008) Cancer-related inflammation. Nature 454:436–444
15. Aliustaoglu M, Bilici A, Ustaalioglu BB et al (2010) The effect of peripheral blood values on prognosis of patients with locally advanced gastric cancer before treatment. Med Oncol 27(4): 1060–1065
16. Crumley AB, McMillan DC, McKernan M et al (2006) An elevated C-reactive protein concentration, prior to surgery, predicts poor cancer-specific survival in patients undergoing resection for gastro-oesophageal cancer. Br J Cancer 94:1568–1571
17. Mohri Y, Tanaka K, Ohi M et al (2010) Prognostic significance of host- and tumor-related factors in patients with gastric cancer. World J Surg 34:285–290. doi:10.1007/s00268-009-0302-1
18. Ray-Coquard I, Cropet C, Van Glabbeke M et al (2009) Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas, and lymphomas. Cancer Res 69: 5383–5391
19. Satomi A, Murakami S, Ishida K et al (1995) Significance of increased neutrophils in patients with advanced colorectal cancer. Acta Oncol 34:69–73
20. Shimada H, Takiguchi N, Kainuma O et al (2010) High preoperative neutrophil-lymphocyte ratio predicts poor survival in patients with gastric cancer. Gastric Cancer 13:170–176
21. Ubukata H, Motohashi G, Tabuchi T et al (2010) Evaluations of interferon-gamma/interleukin-4 ratio and neutrophil/lymphocyte ratio as prognostic indicators in gastric cancer patients. J Surg Oncol 102(7):742–747
22. Yamanaka T, Matsumoto S, Teramukai S et al (2007) The baseline ratio of neutrophils to lymphocytes is associated with patient prognosis in advanced gastric cancer. Oncology 73: 215–220
23. Sobin LH, Wittekind C (eds) (2010) TMN Classification of Malignant Tumours (UICC). Wiley-Blackwell, Chichester, UK
24. Serhan CN, Brain SD, Buckley CD et al (2007) Resolution of inflammation: state of the art, definitions and terms. FASEB J 21:325–332
25. Eck M, Schmausser B, Scheller K et al (2003) Pleiotropic effects of CXC chemokines in gastric carcinoma: differences in CXCL8 and CXCL1 expression between diffuse and intestinal types of gastric carcinoma. Clin Exp Immunol 134:508–515
26. Coussens LM, Tinkle CL, Hanahan D et al (2000) MMP-9 supplied by bone marrow-derived cells contributes to skin carcinogenesis. Cell 103:481–490
27. Kido S, Kitadai Y, Hattori N et al (2001) Interleukin 8 and vascular endothelial growth factor—prognostic factors in human gastric carcinomas? Eur J Cancer 37:1482–1487
28. Yancopoulos GD, Davis S, Gale NW et al (2000) Vascular-specific growth factors and blood vessel formation. Nature 407:242–248
29. Crumley AB, Stuart RC, McKernan M et al (2008) Comparison of an inflammation-based prognostic score (GPS) with performance status (ECOG-ps) in patients receiving palliative chemotherapy for gastroesophageal cancer. J Gastroenterol Hepatol 23:e325–e329
30. McMillan DC (2008) An inflammation-based prognostic score and its role in the nutrition-based management of patients with cancer. Proc Nutr Soc 67:257–262

Surg Today (2011) 41:928–934
DOI 10.1007/s00595-010-4397-7

SURGERY TODAY

Original Article

Influence of Excess Body Weight on the Surgical Outcomes of Total Gastrectomy

DAISUKE NOBUOKA, NAOTO GOTOHDA, YUICHIRO KATO, SHINICHIRO TAKAHASHI, MASARU KONISHI, and TAIRA KINOSHITA

Department of Surgery, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan

Abstract

Purpose. We conducted this retrospective study to identify the influence of excess body weight on the surgical outcome of total gastrectomy (TG) and to evaluate recent advances in this operation.

Methods. The subjects were 644 consecutive gastric cancer patients who underwent TG between 1992 and 2008. Patients with a body mass index (BMI) of 25.0 kg/m^2 or greater were defined as overweight (overweight group) and those with a BMI less than 25.0 kg/m^2 as not overweight (non-overweight group).

Results. The operating times were longer ($P = 0.005$) and intraoperative blood loss was greater ($P < 0.001$) in the overweight group. The incidence of overall postoperative complications ($P = 0.012$) and of pancreatic fistula ($P < 0.001$) were significantly higher in the overweight group. In recent years, we achieved a reduction in operating time ($P < 0.001$), intraoperative blood loss ($P = 0.033$), and incidence of pancreatic fistula ($P = 0.005$), while maintaining curability, in the overweight group.

Conclusions. Although TG for gastric cancer is technically more difficult in overweight patients, they should not be denied this operation. Conversely, we should make a greater effort to improve the surgical outcomes of overweight patients.

Key words Gastric cancer · Total gastrectomy · Overweight · Surgical outcome · Body mass index

Introduction

The proportion of obese and overweight people is increasing steadily over the world.[1] Once considered a problem only in high-income countries, it is now obviously rising in low- and middle-income countries. The World Health Organization (WHO) highlights this nutritional topic as one of the worldwide health crises.[2] Although the prevalence of obesity in Japanese adults has been low compared with that in Western countries,[3] reports using data from the National Nutrition Surveys of Japan show evidence of increasing numbers of overweight adults in Japan.[4] This tendency will certainly continue considering the growing excess fat intake and lack of physical activity. Therefore, Japanese surgeons are more and more often required to operate on overweight patients.[5]

Chemotherapy can prolong the survival of patients with advanced disease, but surgical resection remains the most effective treatment for curable gastric cancer.[6] Based on previous reports that extensive lymph node dissection improved patient survival,[7–9] gastrectomy plus extended systematic lymphadenectomy (D2 resection) has long been the standard treatment in Japan.[10] Despite a recent report indicating that sentinel node navigation surgery may justify limited lymphadenectomy for early disease,[11] removal of metastatic lymph nodes is critically important. However, complete removal of retroperitoneal lymph nodes is technically difficult and not always without risk in overweight patients.[12] Indeed, European studies have shown unfavorable surgical outcomes, partly because of a significantly higher prevalence of overweight patients.[13–15]

Many investigators have found that overweight patients are at risk of a poor outcome after intra-abdominal surgery.[16–18] On the other hand, there have been remarkable advances in surgical techniques in recent years.[18] The purposes of this study were to identify the influence of an overweight state on surgical outcomes and to evaluate recent surgical advances in total gastrectomy (TG).

Reprint requests to: N. Gotohda
Received: December 26, 2009 / Accepted: April 4, 2010

Patients and Methods

Between August 1992 and December 2008, 905 consecutive patients with gastric neoplasm underwent TG at the National Cancer Center Hospital East, Chiba, Japan. Among these 905 patients 892 had gastric cancer, 12 had malignant lymphoma, and 1 had a gastrointestinal stromal tumor. Patients with gastric neoplasms other than gastric cancer and those who underwent resection for residual gastric cancer or palliative resection were excluded from the analysis. Those who underwent other procedures simultaneously, such as hepatectomy, colectomy, portal vein resection, thoracotomy, or intraperitoneal chemotherapy, were also excluded (with the exception of distal pancreaticosplenectomy or splenectomy for gastric cancer and cholecystectomy). The remaining 644 patients were grouped according to time periods (1992–1999 and 2000–2008) for analysis (Fig. 1).

Each patient's height and body weight was measured preoperatively. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2), and categorized according to the WHO cutoff points[2] as follows: underweight, <18.5 kg/m^2; normal range, 18.5–24.9 kg/m^2; preobese, 25.0–29.9 kg/m^2; obese class I, 30.0–34.9 kg/m^2; obese class II, 35.0–39.9 kg/m^2; and obese class III, 40.0 kg/m^2 or greater. We defined the non-overweight group as underweight and normal range, and the overweight group as preobese and obese classes I, II, and III. We then compared the two groups.

All patients underwent open TG, performed or supervised by one of our staff surgeons with extensive experience in gastric surgery. We performed TG with splenectomy (pancreas-preserving method[19]), Japanese-style D2 lymph node dissection, and reconstruction with Roux-en-Y esophagojejunostomy as the standard surgical procedure for advanced gastric cancer located in the upper third of the stomach; TG without splenectomy for early gastric cancer; and TG with pancreaticosplenectomy for patients with direct invasion to the pancreas or evident macroscopic lymph node metastasis along the splenic artery.

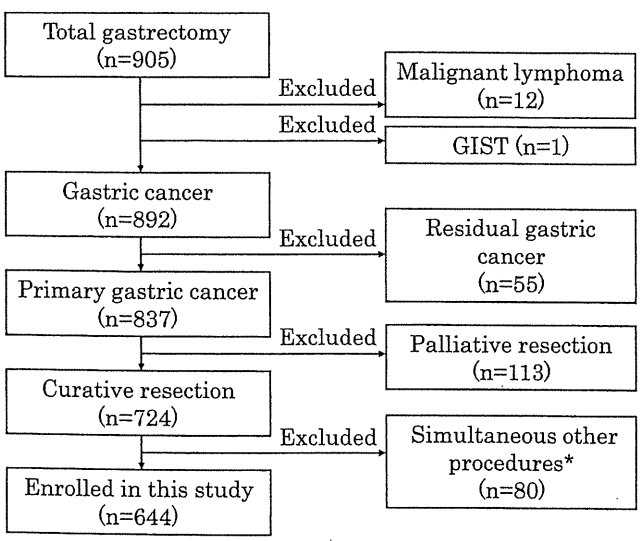


Fig. 1. Schematic flowchart of the enrolled patients. *Hepatectomy, colectomy, portal vein resection, thoracotomy, and intraperitoneal chemotherapy. *GIST*, gastrointestinal stromal tumor

All specimens were routinely sectioned, stained, and checked for cancer progression by experienced pathologists. Pathological stage was assigned according to the Japanese classification of gastric carcinoma, second English edition.[20] Some patients with stage II or more advanced disease received chemotherapeutic drugs as adjuvant therapy, with or without inclusion in clinical trials.[21] When tumor recurrence was discovered, the patients were referred to clinical oncologists and usually received chemotherapy.

Surgical outcomes included operating time, intraoperative blood loss, postoperative complications, postoperative hospital death, duration of hospital stay, and survival time after surgery. Postoperative pancreatic fistula was diagnosed when there was purulent discharge containing necrotic debris from the drainage tube. We included intra-abdominal abscess that might have occurred from pancreatic juice leakage. Anastomotic leakage was diagnosed by radiological examination using orally administered contrast medium. Postoperative hospital death was defined as death from any cause within 30 days after surgery, or death within the same hospital admission.

We used the chi-squared test or Mann–Whitney *U*-test to evaluate differences in patient demographics. Overall and cancer-specific survival curves were obtained by the Kaplan–Meier method and compared by the log-rank test. For all statistical tests, differences with a P value of less than 0.05 were considered significant. Data were analyzed with the statistical package, Dr. SPSS II for Windows (SPSS Japan, Tokyo, Japan).

Results

Among the 644 patients, 65 (10.1%) were underweight, 480 (74.5%) were in the normal range, 95 (14.8%) were preobese, and 4 (0.6%) were in obese class I. No patient was in obese class II or III. Thus, 545 patients (84.6%) were in the non-overweight group and 99 (15.4%) were in the overweight group. The patient characteristics of the two groups are shown in Table 1. The number of patients with earlier stages of disease was significantly higher in the overweight group than in the non-overweight group (P = 0.040). The incidence of diabetes

Table 1. Clinical characteristics of the two groups of patients divided according to body mass index

Factor	Non-overweight (n = 545) (BMI < 24.9)	Overweight (n = 99) (BMI > 25.0)	P value
Sex (male/female)	371/174	77/22	0.054
Age (years)	62.0 ± 10.5	62.0 ± 11.3	0.826
Pathological stage			0.040
IA	87 (16.0)	20 (20.2)	
IB	91 (16.7)	23 (23.2)	
II	115 (21.1)	18 (18.2)	
IIIA	112 (20.6)	19 (19.2)	
IIIB	81 (14.9)	15 (15.2)	
IV	59 (10.8)	4 (4.0)	
Neoadjuvant chemotherapy	45 (8.3)	5 (5.1)	0.273
Diabetes mellitus	45 (8.3)	15 (15.2)	0.030
Operative procedure			0.384
TG without splenectomy	108 (19.8)	28 (28.3)	
TG with splenectomy	394 (72.3)	59 (59.6)	
TG with pancreaticosplenectomy	43 (7.9)	12 (12.1)	

Values are expressed as mean ± standard deviation
BMI, body mass index; TG, total gastrectomy

Table 2. Early surgical outcomes of the two groups of patients divided according to body mass index

Factor	Non-overweight (n = 545)	Overweight (n = 99)	P value
Operating time (min)	245.1 ± 69.3	265.9 ± 74.1	0.005
Intraoperative blood loss (ml)	651.9 ± 454.4	951.6 ± 664.8	<0.001
Postoperative complication	192 (35.2)	48 (48.5)	0.012
Pancreatic fistula	95 (17.4)	33 (33.3)	<0.001
Anastomotic leakage	25 (4.6)	5 (5.1)	0.501
Wound infection	22 (4.0)	6 (6.1)	0.250
Pneumonia	10 (1.8)	6 (6.1)	0.025
Postoperative hospital death	3 (0.6)	1 (1.0)	0.488
Postoperative hospital stay (days)	25.1 ± 16.2	35.5 ± 33.9	0.059

Values are expressed as mean ± standard deviation

mellitus was significantly higher in the overweight group than in the non-overweight group (P = 0.030). There was no significant difference in operative procedures between the groups (P = 0.384).

The early surgical outcomes of the two groups are shown in Table 2. The mean operating time was approximately 20 min longer (265.9 vs 245.1 min., P = 0.005) and the mean intraoperative blood loss was approximately 300 ml greater (951.6 vs 651.9 ml, P < 0.001) in the overweight group than in the non-overweight group. The incidence of overall surgery-related complications was significantly higher in the overweight group than in the non-overweight group (48.5% vs 35.2%, P = 0.012), mainly because of the higher incidence of pancreatic fistula in the overweight group (33.3% vs 17.4%, P < 0.001). Mean postoperative hospital stay was approximately 10 days longer in the overweight group, but the difference was not significant (35.5 vs 25.1 days, P = 0.059).

The overall survival curves of the two groups are shown in Fig. 2. There was no significant difference in survival among patients with stage IA (P = 0.281), IB (P = 0.766), II (P = 0.712), IIIA (P = 0.238), or IIIB (P = 0.829) disease between the two groups. In contrast, patients in the overweight group had significantly worse survival than those in the non-overweight group at stage IV (P = 0.045). Similarly, cancer-specific survival did not differ significantly for stage IA (P = 0.488), IB (P = 0.969), II (P = 0.879), IIIA (P = 0.368), or IIIB (P = 0.659) disease, although it was slightly better in the overweight group at stages IA, IB, II, and IIIA. All patients with stage IV gastric cancer died of the disease; thus, cancer-specific survival at stage IV was the same as overall survival (P = 0.045). The number of patients who died of comorbidity in the overweight group (11/99, 11.1%) exceeded that in the non-overweight group (35/545, 6.4%), but the difference was not significant (P = 0.096). Overall and cancer-specific survival in the overweight group at overall disease stages was better than that in the non-overweight group, but the difference was not significant (P = 0.473, overall survival; P = 0.124, cancer-specific survival).

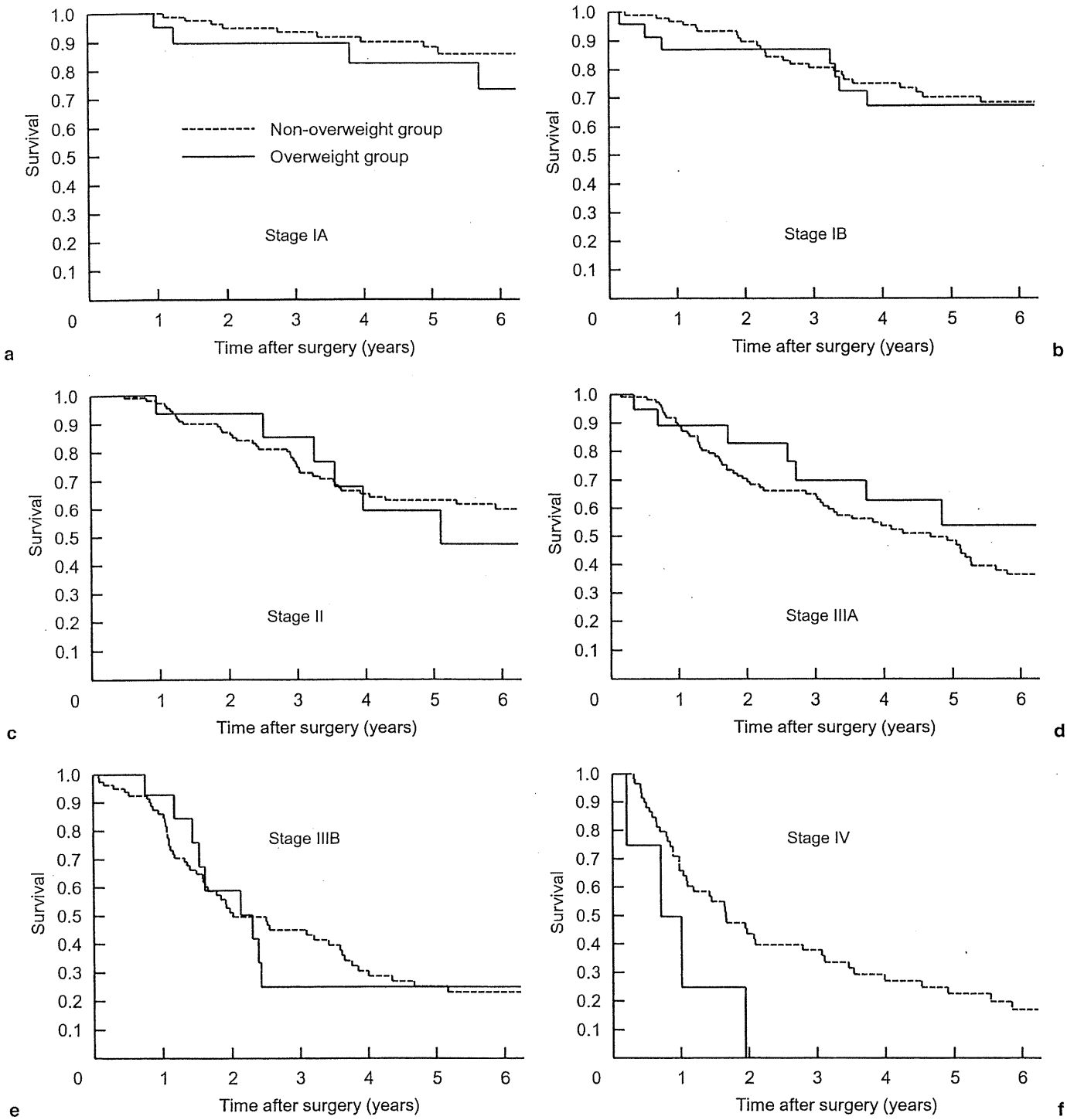
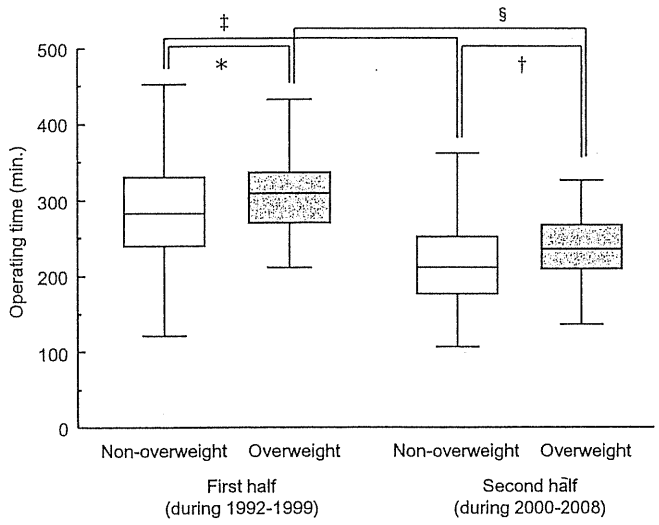
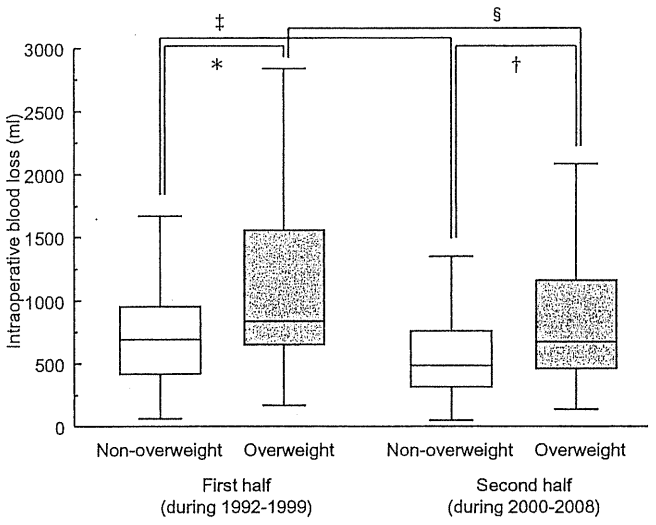


Fig. 2a–f. Overall survival curves of the overweight and non-overweight patients with **a** stage IA, **b** stage IB, **c** stage II, **d** stage IIIA, **e** stage IIIB, and **f** stage IV disease. *Solid line*, overweight group; *dashed line*, non-overweight group. **a** $P = 0.281$, **b** $P = 0.766$, **c** $P = 0.712$, **d** $P = 0.238$, **e** $P = 0.829$, **f** $P = 0.045$ (log-rank test)

The changes in intraoperative outcomes according to BMI in two different periods are shown in Fig. 3. In recent years, the operating time has become shorter ($P < 0.001$, non-overweight group; $P < 0.001$, overweight group) and intraoperative blood loss has decreased ($P < 0.001$, non-overweight group; $P = 0.033$, overweight group) in both groups. Nevertheless, the differences in operating time ($P = 0.024$, first period; $P = 0.003$, second

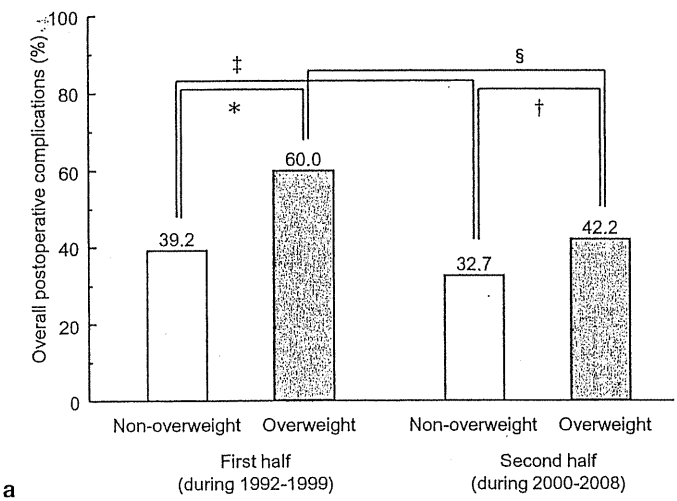


a

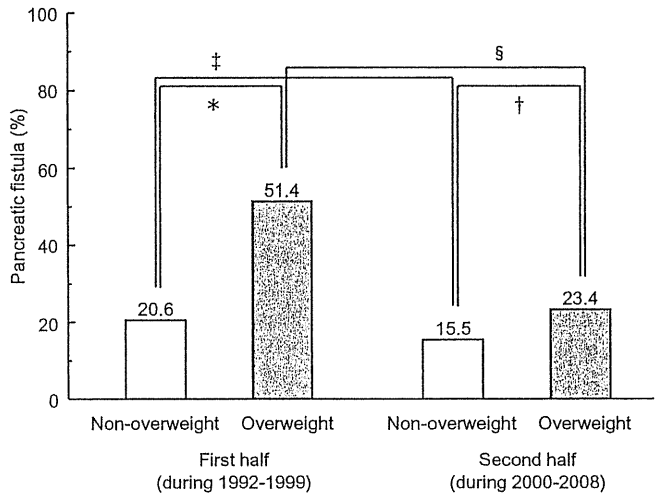


b

Fig. 3a,b. Intraoperative outcomes according to body mass index in the early and latter periods of this study. **a** Operating time. *P = 0.024, †P = 0.003, ‡P < 0.001, §P < 0.001 (Mann–Whitney U-test). **b** Intraoperative blood loss. *P = 0.002, †P < 0.001, ‡P < 0.001, §P = 0.033 (Mann–Whitney U-test)



a



b

Fig. 4a,b. Postoperative complications according to body mass index in the early and latter periods of this study. **a** Overall postoperative complications. *P = 0.021, †P = 0.144, ‡P = 0.123, §P = 0.090 (chi-squared test). **b** Pancreatic fistula. *P < 0.001, †P = 0.118, ‡P = 0.127, §P = 0.005 (chi-squared test)

period) and intraoperative blood loss (P = 0.002, first period; P < 0.001, second period) between the groups remain significant.

The changes in postoperative complications according to BMI in the two different periods are shown in Fig. 4. In recent years, the incidence of pancreatic fistula has decreased significantly in the overweight group (P = 0.005). Although the incidence of overall postoperative complications and of pancreatic fistula in particular were significantly higher in the overweight group in the first period (P = 0.021, overall postoperative complications; P < 0.001, pancreatic fistula), the differences were not significant in the second period (P = 0.144, overall postoperative complications; P = 0.118, pancreatic fistula).

Discussion

There is much evidence that being overweight increases the risk of cardiac gastric cancer, possibly caused by higher abdominal pressure and the resulting gastroesophageal reflux.[22,23] Indeed, the incidence of cardiac cancer has gradually increased with the prevalence of overweight adults in Western countries.[24] Although in Japan most gastric cancers originate in the middle or lower third of the stomach,[25] cancers originating in the

cardiac area may increase in the future; hence, the importance of TG globally is growing.

In Japan, gastrectomy with extended (D2) lymph node dissection is the standard treatment for curable gastric cancer.[10] However, excessive adipose tissue makes this procedure more difficult.[12] According to a previous report, insufficient lymph node dissection in overweight patients may leave metastatic nodes behind, resulting in a poor prognosis.[26] In the present study on a large number of consecutive gastric cancer patients who underwent TG with curative intent, a significant difference in overall and cancer-specific survival rate was observed between the overweight and non-overweight groups only for stage IV disease, for which the sample size was too small for the result to be accepted. Although we confirmed that the surgical technique for lymph node dissection at our institution was acceptable for overweight patients, because there was no statistical difference in the survival rate and number of patients who died of comorbidity, TG, which is a kind of weight-reduction surgery, may prevent death from comorbidity in overweight patients. Moreover, a better survival rate after curative gastrectomy, especially for early-stage gastric cancer, in overweight patients has been reported recently.[27] It has also been speculated that overweight patients who lose weight after gastrectomy may achieve ideal body weight years after surgery, possibly resulting in a better prognosis. Similarly, in the present study, although the difference was not significant, both overall and cancer-specific survival at all disease stages was slightly better in the overweight group. Early surgical outcomes have improved in recent years. We reduced both the operating time and intraoperative blood loss in both the overweight and non-overweight groups because our surgical team gained enough experience in gastric surgery to make our hospital become a high-volume center. However, there was still a significant difference between the groups because TG is technically more difficult in overweight patients.

Pancreatic fistula was the most frequent postoperative complication in this study, especially in the overweight group. Multivariate analysis in our previous study showed that BMI and operative procedure (pancreatic resection) were independent risk factors for pancreatic fistula.[18] We have attempted to prevent pancreatic fistula, using such means as total preservation of the splenic artery in TG with splenectomy and by using a linear stapling device to close the cut end of the pancreas in TG with pancreaticosplenectomy. The incidence of pancreatic fistula decreased significantly in the overweight group in the latter years, so that the incidence of postoperative complications in the overweight group became as low as that in the non-overweight group. There have been remarkable advances in surgical techniques in recent years.

The criterion for obesity or overweight is controversial, as BMI does not necessarily measure the body fat volume.[28] Thus, a recent study revealed the utility of abdominal imaging by multidetector-row computed tomography,[29] another suggested waist circumference,[30] and another advocated the waist–hip ratio.[31] We selected BMI because it is the most universally acknowledged criterion,[32,33] and data are readily available for routine clinical use.

The difference in the prevalence and degree of "overweight" between Japan and Western countries limited this study. Although we demonstrated the effectiveness of our surgical techniques for overweight gastric cancer patients in Japan, we could not establish whether they would be effective for severely obese patients in Western countries.

In conclusion, we reduced the operating time, intraoperative blood loss, and rate of postoperative complications while maintaining the curability of TG for gastric cancer. Although TG is technically more difficult to perform in overweight patients with gastric cancer, they should not be denied this surgical treatment and we should make more effort to improve their surgical outcomes.

References

1. Popkin BM, Doak CM. The obesity epidemic is a worldwide phenomenon. Nutr Rev 1998;56:106–14.
2. World Health Organization. Obesity: preventing and managing the global epidemic. WHO obesity technical report series 894. Geneva, Switzerland: World Health Organization; 2000.
3. Noguchi Y, Yoshikawa T, Tsuburaya A, Motohashi H, Karpeh MS, Brennan MF. Is gastric carcinoma different between Japan and the United States? Cancer 2000;89:2237–46.
4. Yoshiike N, Seino F, Tajima S, Arai Y, Kawano M, Furuhata, et al. Twenty-year changes in the prevalence of overweight in Japanese adults: The National Nutrition Survey 1976–95. Obes Rev 2002;3: 183–90.
5. Kubo M, Sano T, Fukunaga T, Katai H, Sasako M. Increasing body mass index in Japanese patients with gastric cancer. Gastric Cancer 2005;8:39–41.
6. Catalano V, Labianca R, Beretta GD, Gatta G, de Braud F, Van Cutsem E. Gastric cancer. Crit Rev Oncol Hematol 2005;54:209–41.
7. Siewert JR, Bottcher K, Stein HJ, Roder JD. Relevant prognostic factors in gastric cancer: ten-year results of the German Gastric Cancer Study. Ann Surg 1998;228:449–61.
8. Roukos DH, Lorenz M, Encke A. Evidence of survival benefit of extended (D2) lymphadenectomy in western patients with gastric cancer based on a new concept: a prospective long-term follow-up study. Surgery 1998;123:573–8.
9. Wu CW, Hsiung CA, Lo SS, Hsieh MC, Chen JH, Li AF, et al. Nodal dissection for patients with gastric cancer: a randomised controlled trial. Lancet Oncol 2006;7:309–15.
10. Nakajima T. Gastric cancer treatment guidelines in Japan. Gastric Cancer 2002;9:278–86.
11. Ohdaira H, Nimura H, Takahashi N, Mitsumori N, Kashiwagi H, Narimiya N, et al. The possibility of performing a limited resection and a lymphadenectomy for proximal gastric carcinoma based on sentinel node navigation. Surg Today 2009;39:1026–31.

12. Dhar DK, Kubota H, Tachibana M, Kotoh T, Tabara H, Masunaga R, et al. Body mass index determines the success of lymph node dissection and predicts the outcome of gastric carcinoma patients. Oncology 2000;59:18–23.
13. Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. Lancet 1996;347:995–9.
14. Hartgrink HH, van de Velde CJ, Putter H, Bonenkamp JJ, Klein Kranenbarg E, Songun I, et al. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. J Clin Oncol 2004;22: 2069–77.
15. Bonenkamp JJ, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JT, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. Lancet 1995;345:745–8.
16. Inagawa S, Adachi S, Oda T, Kawamoto T, Koike N, Fukao K. Effect of fat volume on postoperative complications and survival rate after D2 dissection for gastric cancer. Gastric Cancer 2000;3: 141–4.
17. Tsujinaka T, Sasako M, Yamamoto S, Sano T, Kurokawa Y, Nashimoto A, et al. Influence of overweight on surgical complications for gastric cancer: results from a randomized control trial comparing D2 and extended para-aortic D3 lymphadenectomy (JCOG9501). Ann Surg Oncol 2007;14:355–61.
18. Nobuoka D, Gotohda N, Konishi M, Nakagohri T, Takahashi S, Kinoshita T. Prevention of postoperative pancreatic fistula after total gastrectomy. World J Surg 2008;32:2261–6.
19. Maruyama K, Sasako M, Kinoshita T, Sano T, Katai H, Okajima K. Pancreas-preserving total gastrectomy for proximal gastric cancer. World J Surg 1995;19:532–6.
20. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma (2nd English ed.). Gastric Cancer 1998;1: 10–24.
21. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007;357:1810–20.
22. Lindblad M, Rodríguez LA, Lagergren J. Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study. Cancer Causes Control 2005;16:285–94.
23. Lagergren J, Bergström R, Nyrén O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. Ann Intern Med 1999;130:883–90.
24. Orengo MA, Casella C, Fontana V, Filiberti R, Conio M, Rosso S, et al. Trends in incidence rates of oesophagus and gastric cancer in Italy by subsite and histology, 1986–1997. Eur J Gastroenterol Hepatol 2006;18:739–46.
25. Japanese Gastric Cancer Association Registration Committee. Gastric cancer treated in 1991 in Japan: data analysis of nationwide registry. Gastric cancer 2006;9:51–66.
26. Adachi W, Kobayashi M, Koike S, Rafique M, Nimura Y, Kuroda T, et al. The influence of excess body weight on the surgical treatment of patients with gastric cancer. Surg Today 1995;25:939–45.
27. Tokunaga M, Hiki N, Fukunaga T, Ohyama S, Yamaguchi T, Nakajima T. Better 5-year survival rate following curative gastrectomy in overweight patients. Ann Surg Oncol 2009;16:3245–51.
28. Prentice AM, Jebb SA. Beyond body mass index. Obes Rev 2001;2:141–7.
29. Tokunaga M, Hiki N, Fukunaga T, Ogura T, Miyata S, Yamaguchi T. Effect of individual fat areas on early surgical outcomes after open gastrectomy for gastric cancer. Br J Surg 2009;96:496–500.
30. Pi-Sunyer FX. Obesity: criteria and classification. Proc Nutr Soc 2000;59:505–9.
31. Srikanthan P, Seeman TE, Karlamangla AS. Waist–hip-ratio as a predictor of all-cause mortality in high-functioning older adults. Ann Epidemiol 2009;19:724–31.
32. Choban PS, Flancbaum L. The impact of obesity on surgical outcomes: a review. J Am Coll Surg 1997;185:593–603.
33. Bray GA, Bellanger T. Epidemiology, trends, and morbidities of obesity and the metabolic syndrome. Endocrine 2006;29:109–17.

Jpn J Clin Oncol 2011;41(9)1079–1085
doi:10.1093/jjco/hyr103

Surgical Outcomes of Multicentric Adenocarcinomas of the Biliary Tract

Shin Kobayashi[1], Masaru Konishi[1,*], Yuichiro Kato[1], Naoto Gotohda[1], Shinichiro Takahashi[1], Takahiro Kinoshita[1], Taira Kinoshita[1] and Motohiro Kojima[2]

[1]Department of Surgical Oncology, National Cancer Center Hospital East, and [2]Department of Pathology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

*For reprints and all correspondence: Masaru Konishi, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan. E-mail: mkonishi@east.ncc.go.jp

Received April 9, 2011; accepted June 20, 2011

Objective: In comparison to single biliary cancers, distinct features of biliary multicentric adenocarcinomas are not yet clear.
Methods: From July 1992 to July 2009, 393 patients underwent surgery for cancers of the biliary tract at the National Cancer Center Hospital East, Kashiwa, Japan. Clinicopathological characteristics and surgical outcomes of multicentric biliary adenocarcinoma were compared with those of single cancers.
Results: During the period, 10 cases (2.5%) with multicentric cancer (6 synchronous and 4 metachronous cancers) were found among 393 cases of biliary cancer. Pathologically, compared with single cancers, multicentric adenocarcinomas were more likely to be early cancers and to be papillary carcinomas with both superficial epithelial tumor spread and extensive dysplastic epithelium, but were less likely to have lymph node metastases ($P < 0.01$). The proportion of multicentric cancers among early papillary cancers was high (9/24, 37.5%). Clinically, no recurrences were detected in lymph nodes, peritoneum or distant organs, but one recurrence in the remnant bile duct. Only one patient died from cancer progression. The overall survival of patients with multicentric adenocarcinomas was statistically the same as that of single cancers (median survival: 69 vs. 30 months, $P = 0.47$).
Conclusions: Multicentric adenocarcinomas of the biliary tract have distinct features compared with single cancers.

Key words: multicentric adenocarcinoma – biliary tract – cancer – surgery

INTRODUCTION

Multicentric adenocarcinoma of the biliary tract is very rare. Its highest reported incidence has been 3.7% (1). There have been only a small number of anecdotal case reports regarding clinicopathological characteristics and surgical outcomes of multicentric adenocarcinomas of the biliary tract (1–8). Some argue that pancreaticobiliary maljunction (PBM) is associated with multicentric biliary adenocarcinoma, while others do not (1–4,9). Okamoto et al. (10) reported that papillary adenocarcinoma was associated with multicentric cancer of the extrahepatic bile duct. However, the distinct features of biliary multicentric adenocarcinoma are not clear in comparison with single cases. In this analysis, clinicopathological features and surgical outcomes of multicentric adenocarcinomas of the biliary tract are described, especially in comparison with single cases. The purpose of this study was: (i) to describe distinct clinicopathological features of multicentric adenocarcinomas of the biliary tract; (ii) to clarify long-term outcomes after surgery for biliary multicentric adenocarcinomas; and (iii) to discuss surgical treatment strategies for multicentric adenocarcinomas.

PATIENTS AND METHODS

From July 1992 to July 2009, 393 patients underwent surgery for biliary tract cancers at the Department of

Surgery, National Cancer Center Hospital East (NCCHE), Kashiwa, Japan. Biliary tract cancers included intrahepatic cholangiocellular carcinoma, extrahepatic bile duct carcinoma, gallbladder carcinoma and papilla of Vater carcinoma. Among those 393 consecutive patients, patients with multicentric adenocarcinoma, either synchronous or metachronous, were enrolled in this study. Clinicopathological characteristics and surgical outcomes of multicentric adenocarcinomas of the biliary tract were retrospectively analyzed and compared with those of single lesions.

Definition of Multicentric Adenocarcinoma

Synchronous multicentric adenocarcinoma was defined as multiple lesions without continuity between each other as pathologically diagnosed from surgical specimens. Criteria of metachronous multicentric adenocarcinoma were as follows: (i) the first lesion was pathologically diagnosed from a surgical specimen, (ii) the second lesion was pathologically or clinically diagnosed with an interval of more than 5 years after the initial surgery, (iii) the second lesion needed to be far away from the resection margin of the initial surgery. If the second lesion was diagnosed within 5 years after the initial surgery or if it developed on the resection margin of the initial surgery, recurrence, not multicentric adenocarcinoma, was diagnosed.

Pathological Examination

Each surgical specimen was examined by two independent experienced pathologists at NCCHE. Each tumor was pathologically diagnosed according to the general rules of bile duct cancer of the Japanese Biliary Association (11). Specifically, papillary adenocarcinoma was defined as tumor cells proliferating and protruding with a fine fibrovascular core; tubular adenocarcinoma was defined as tumor cells proliferating with atypical tubular gland formation; and early cancer was defined as not invading beyond the fibromuscular layer of the bile duct, the muscular layer of gallbladder or the sphincter of Oddi at the papilla of Vater (11).

Clinical Diagnosis

Patients' data were reviewed by hepato-pancreatico-biliary surgeons, medical oncologists and interventional radiologists during a conference to determine treatment strategies for each patient. When the second lesion of the metachronous multicentric cancer could not be pathologically examined, it was diagnosed clinically with the agreement at the above conference.

Long-term Outcomes After Surgery

Recurrence and survival were compared between patients with multicentric adenocarcinoma and those with a single lesion. Recurrence was diagnosed by elevation of tumor marker and radiological imaging studies such as computed tomography (CT), magnetic resonance imaging, ultrasound and cholangiography. Recurrence was analyzed in patients in whom resection without any residual tumor (R0) was achieved according to the classification of the International Union against Cancer (12). Location of recurrence was divided into five sites as follows: remnant bile duct, lymph node, local, peritoneum and distant organs (Fig. 1). Remnant bile duct recurrence was defined as a recurrent tumor that was with intraductal growth without peripheral soft tissue change seen by CT. Remnant bile duct recurrence needed to happen apart from the resection margin of the initial surgery; otherwise, it was classified as local recurrence. Local recurrence included anastomotic recurrence and soft tissue recurrence in which soft tissue around original tumor displayed increased density with contrast enhancement by CT. If the recurrence developed on the anastomotic site, it was considered to be local recurrence and not remnant bile duct recurrence. Overall survival time was calculated after the date of the initial surgery.

Statistical Analysis

All data were recorded in a database for analysis (Microsoft Excel and SPSS 11.0 J for Windows). Differences between numerical variables were analyzed by the Mann–Whitney *U*-test and those between categorical variables were analyzed by χ^2 statistics. Survival analyses were performed by using the Kaplan–Meier method, and differences between the curves were tested by using the log-rank test (SPSS 11.0 J for Windows). A P-value of <0.05 was considered statistically significant.

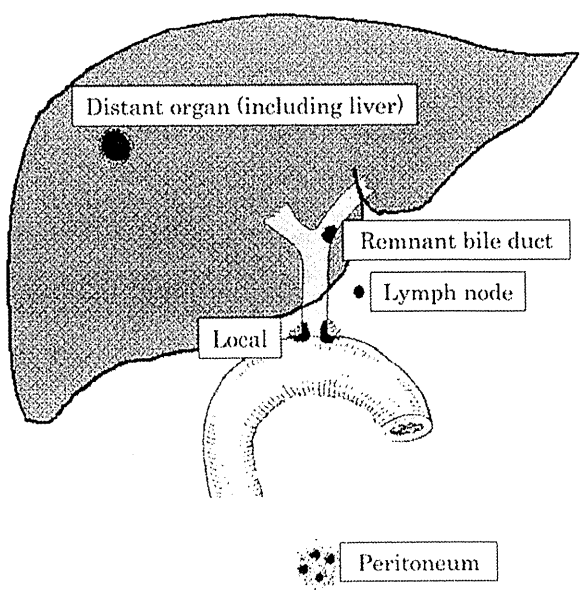


Figure 1. Schematic drawing of five recurrent sites. The schema is the one after pancreaticoduodenectomy with choledochojejunostomy.

RESULTS

Among 393 consecutive patients who underwent surgery for biliary tract cancers at NCCHE from 1992 to 2009, 10 patients (2.5%) were diagnosed with multicentric adenocarcinoma in the biliary tract. Therefore, a total of 403 lesions were included in this study. The focus of the lesions was as follows: intrahepatic bile duct ($n = 70$), extrahepatic bile duct ($n = 177$), gallbladder ($n = 81$) and papilla of Vater ($n = 75$). Among those 403 lesions, 3 multicentric lesions could not be pathologically examined at NCCHE. One of the three lesions was pathologically diagnosed at a referral hospital, and the other two lesions were clinically diagnosed at a multidisciplinary conference by characteristic CT findings. Among 10 cases with multicentric adenocarcinomas, 6 were synchronous and 4 were metachronous; there were 7 male patients and 3 female patients, and the median age was 71 years. Clinicopathological factors of the six patients with synchronous multicentric adenocarcinomas are described in Table 1 and those of the four patients with metachronous multicentric adenocarcinoma are described in Table 2. All multicentric lesions that were pathologically examined at NCCHE ($n = 17$) were papillary adenocarcinomas or tubular adenocarcinomas according to the general rules of bile duct cancer of the Japanese Biliary Association (11). In particular, papillary adenocarcinoma was found in 12 of the 17 lesions and it was the dominant pathological type in 10 lesions. Depth of tumor invasion was within the mucosa ($n = 5$) or the fibromuscular layer ($n = 9$), and only three lesions invaded the subserosal layer. Lymph node metastasis was identified in only one patient (Table 1, Case #1). A total of 13 lesions exhibited superficial epithelial tumor spread around the main focus of the lesion. Those superficial epithelial tumor spreads were diffusely surrounded by dysplastic mucosa. In synchronous multicentric cancers, there was no continuity of the superficial epithelial tumor spread between each lesion as in the definition, but dysplastic mucosa intermittently and sometimes continuously extended between each superficial epithelial tumor. A typical example of synchronous multicentric adenocarcinoma (Table 1, Case #4) is shown in Fig. 2.

Chronology of surgical outcomes is described in Fig. 3. R0 resection was achieved in all but one resection (Table 2, first operation of Case #4). Among those 11 R0 resections, there were two recurrences (Table 1, Cases #1 and #6) and three metachronous cancers (Table 2, Cases #1, #2 and #3). One recurrence (Table 1, Case #6) developed in the remnant bile duct and was treated with chemotherapy, and the other (Table 1, Case #1) had local recurrence and was treated with best supportive care. A total of two of the four metachronous cases (Table 2, Cases #2 and #4) could not undergo the second procedure due to multicentric second lesions (Case #2) and advanced age (Case #4). These two cases were treated with chemotherapy (Case #2) and best supportive care (Case #4). There were a total of five deaths during the follow-up period. One death was treatment-related (Table 2, Case #3; post-operative liver failure), one was disease-related (Table 1, Case #1; cholangitis caused by local recurrence), two were due to chronic or emergent diseases (Table 1, Cases #1 and #4) and only one death was due to cancer progression (Table 1, Case #6; remnant bile duct recurrence caused repeated obstructive cholangitis and was followed by death from cancer progression).

Table 1. Clinicopathological findings of six patients with synchronous multicentric biliary adenocarcinoma

Case	Age/sex	Procedure	Tumor location	Histology/depth	Superficial spread and dysplasia	Recurrence	Survival	Cause of death
1	78/M	EHBDR	Gb	tub2/ss	+	Local	Dead (1yr1mo)	Cholangitis
			Bm	tub2/ss	+			
2	71/F	Ex.LHx	Bm	pap/fm	+		Alive (1yr7mo)	
			Bi	pap/fm	−			
3	53/M	EHBDR	Bi	tub1/fm	−		Alive (10mo)	
			Bm	tub1/m	−			
4	73/M	SSpPD	Gn	pap/ss	+		Dead (2yr5mo)	General malaise
			Bi	pap/fm	+			
5	70/M	EHBDR	Gn	tub2 + pap/fm	+		Alive (2yr7mo)	
			C	tub1/m	−			
6	72/M	SSpPD	C	pap/fm	+	Remnant bile duct (Br)	Dead (1yr5mo)	Cancer progression
			Bi	pap + tub2/fm	+			

EHBDR, extrahepatic bile duct resection; Gb, gallbladder body; tub2, moderately differentiated tubular adenocarcinoma; ss, subserosal layer; yr, years; mo, months; Bm, middle third of extrahepatic bile duct; Ex.LHx, extended left hemihepatectomy; pap, papillary adenocarcinoma; fm, fibromuscular layer; Bi, lower third of extrahepatic bile duct; tub1, well-differentiated tubular adenocarcinoma; m, mucosal layer; Gn, gallbladder neck; SSpPD, subtotal stomach preserving pancreaticoduodenectomy; Br, right hepatic duct.

Table 2. Clinicopathological findings of four patients with metachronous multicentric biliary adenocarcinoma

Case	#	Age/sex	Procedure	Tumor location	Histology/depth	Superficial spread and dysplasia	Survival	Cause of death
1	1st	65/F	LHx	IHBD(Lt.lobe)	NA/m	NA	Dead (6yr9m)	Pancreatitis
	2nd	71	SSpPD	Br	pap/fm	+		
2	1st	67/M	Ex.LHx	IHBD(B2/3/4)	pap + tub1/fm	+	Alive (8yr4m)	
	2nd	72	—	IHBD(multiple)	NA	NA		
3	1st	73/F	Ex.LHx	IHBD(B4)	pap/m	+	Dead (5yr9m)	Liver failure
	2nd	78	AHx	IHBD(B8)	pap/m	+		
4	1st	80/M	Ex.RHx	Br	tub1 + pap/fm	+	Alive (9yr9m)	
	2nd	90	—	IHBD(B4)	NA	NA		

LHx, left hepatectomy; IHBD, intrahepatic bile duct; NA, not available; m, mucosal layer; SSpPD, subtotal stomach preserving pancreaticoduodenectomy; Br, right hepatic duct; pap, papillary adenocarcinoma; fm, fibromuscular layer; Ex.LHx, extended left hepatectomy; B2/3/4, confluence of intrahepatic subsegmental bile duct 2/3/4; pap, papillary adenocarcinoma; tub1, well-differentiated tubular adenocarcinoma; AHx, anterior segmentectomy; Ex.RHx, extended right hepatectomy.

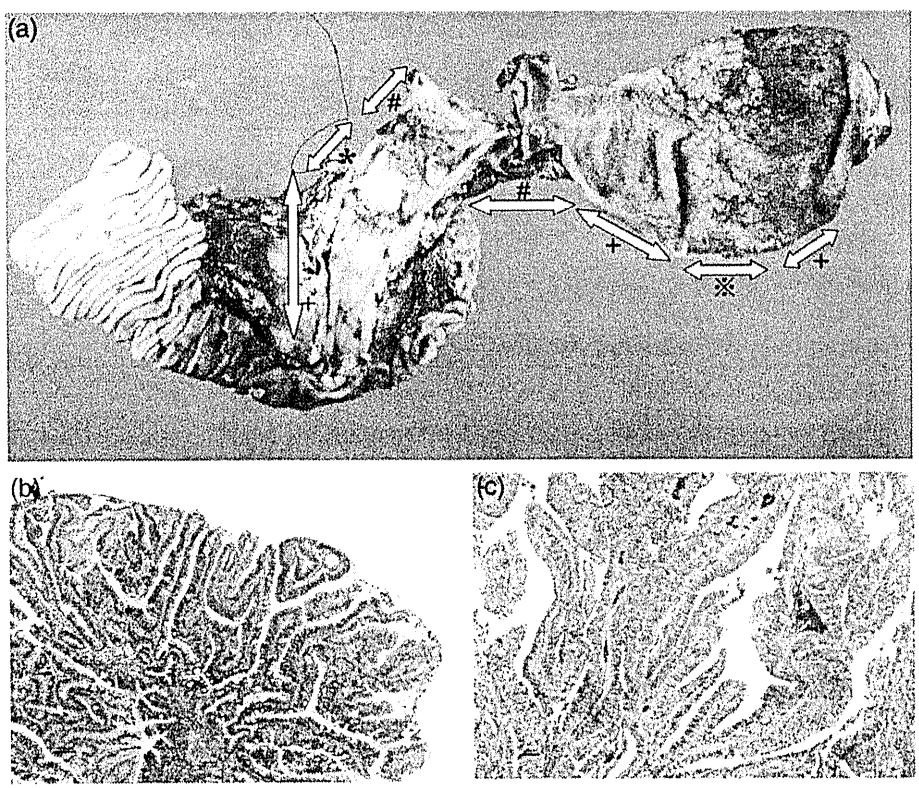


Figure 2. A typical example of synchronous multicentric adenocarcinoma of the biliary tract [(a) macroscopic view, (b and c) stained with hematoxylin and eosin, ×100 magnification]. (a) Extrahepatic bile duct adenocarcinoma (*) and gallbladder adenocarcinoma (※) were identified synchronously. Each tumor was accompanied with superficial tumor spread (+). Dysplastic mucosa (#) diffusely surrounded the superficial tumor spread. (b) A pathological specimen of the extrahepatic bile duct adenocarcinoma is shown. Tumor cells with a high nuclear cytoplasm ratio proliferate and protrude with a fine fibrovascular core. This lesion was diagnosed as papillary adenocarcinoma according to the general rules of bile duct cancer of the Japanese Biliary Association (11). The depth of invasion was the fibromuscular layer. (c) A pathological specimen of gallbladder adenocarcinoma is shown. Tumor cells proliferate and protrude with a fine fibrovascular core, and this lesion was diagnosed as papillary adenocarcinoma as well. The depth of invasion was the subserosal layer.

Clinicopathological and surgical outcomes were compared between multicentric cases and single cases, as is seen in Table 3. Papillary adenocarcinoma and early cancer were significantly more frequent in multicentric cases ($P < 0.01$), while lymph node metastasis was more frequently observed in single cases ($P = 0.01$). R0 resection was achieved in

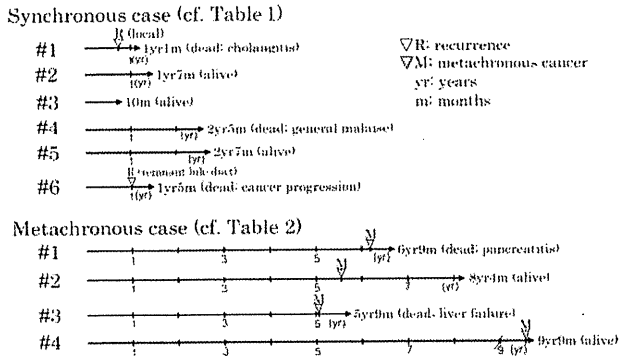


Figure 3. Chronological outcomes of each patient with multicentric cancers. Development of recurrences, metachronous cancers and survival are described chronologically. Each case number corresponds to that of each table. Survival time (year) is calculated from the date of initial surgery.

Table 3. Clinicopathological comparison between multicentric and single cancers

	Multicentric cancers (case = 10, resection = 12, lesion = 17)	Single cancers (case = resection = lesion = 383)	*P* value
Sex: male[a]	7 (70.0%)	226 (59.0%)	0.36
Age (years)[b]	72 (53–80)	67 (39–89)	0.11
CEA (ng/ml)[b]	2.7 (1.0–3.7)	2.8 (0.2–435)	0.32
CA19-9 (U/ml)[b]	34 (9–10,147)	58 (0–78,020)	0.55
Cancers in other organs[a]	2 (20.0%)	57 (14.9%)	0.46
Papillary carcinoma[c]	10 (58.8%)	63 (16.4%)	<0.01
Early cancer[c]	14 (82.4%)	39 (10.2%)	<0.01
LNM[b]	1 (8.3%)	188 (49.1%)	<0.01
R0 resection[b]	11 (91.7%)	299 (88.1%)	0.32
Recurrence[b,d]	2 (18.2%)	144 (48.2%)	0.55

CEA, carcino-embryonic antigen; CA19-9, carcino antigen 19-9; LNM, lymph node metastasis; R0, resection without any residual tumor (12).
[a]The variable was compared among each case (the number of multicentric cases was 10).
[b]The variables were compared among each resection (the number of resections in multicentric cases was 12).
[c]The variables were compared among each lesion (the number of lesions in multicentric cases was 17).
[d]Recurrence was analyzed in patients with R0 resection (12).

about 90% of cases in both groups. Regarding recurrence after R0 resection among patients with multicentric adenocarcinoma, remnant bile duct recurrence was identified in one patient and no recurrence developed in the lymph nodes, peritoneum or distant organs as an initial site (Table 4). The PBM was not identified among multicentric cases, whereas there were five cases with PBM among single cases ($P = 0.88$).

A survival curve of patients with multicentric adenocarcinoma was compared with that of single cases in Fig. 4. The median survival time (MST) of multicentric cases was 69 months [95% confidence interval (CI): 9–129 months] and 30 months (95% CI: 24–36 months) in single cases ($P = 0.47$). Three- and 5-year survival rates were both 54.9% in multicentric cases and were 44.4 and 34.5% in single cases, respectively. No statistical difference was identified between multicentric cases and single cases ($P = 0.47$). The median follow-up time was 22 months.

Table 4. Comparison of initial recurrence after R0 resection between multicentric and single cancers (the number of R0 resections was 11 in multicentric cancers and 299 in single cancers as in Table 3)

	Multicentric cancers ($n = 9$)	Single cancers ($n = 35$)
Early cancers ($n = 44$)		
Remnant bile duct	1 (11.1%)	0
Lymph node	0	0
Local	0	0
Peritoneum	0	0
Distant organ	0	1 (2.9%)
	Multicentric cancers ($n = 2$)	**Single cancers ($n = 264$)**
Advanced cancers ($n = 266$)		
Remnant bile duct	0	0
Lymph node	0	52 (19.7%)
Local	1 (50.0%)	22 (8.3%)
Peritoneum	0	29 (11.0%)
Distant organ	0	102 (38.6%)

R0, resection without any residual tumor according to the classification of the International Union Against Cancer (12).

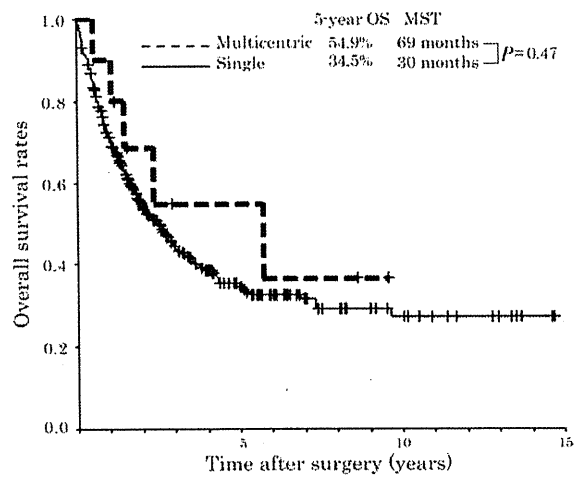


Figure 4. Comparison of survival curves of patients with multicentric adenocarcinoma and single cases. Overall survival (OS) of multicentric adenocarcinoma was not significantly different from OS of single cases ($P = 0.47$).

DISCUSSION

Multicentric adenocarcinoma of the biliary tract is rare, and there have been only several anecdotal case reports so far (1–5). Clinicopathological characteristics of multicentric biliary adenocarcinoma and long-term outcomes after surgery have not been discussed in detail. In this analysis, 10 cases of multicentric adenocarcinoma were found among 393 consecutive cases of biliary adenocarcinoma. To the best of our knowledge, this is the largest reported case series. The incidence of multicentric adenocarcinoma was 2.5% ($n = 10$, 6 synchronous and 4 metachronous cases), similar to previous findings of 3.7% (1).

Clinicopathological analysis has revealed that multicentric adenocarcinomas of the biliary tract have distinct features compared with other single cancers (Table 3). Pathologically, multicentric adenocarcinomas were more likely to be papillary adenocarcinomas and early cancers and were less likely to have lymph node metastasis than single cancers ($P < 0.01$). Among 72 lesions in which papillary carcinomas were the dominant pathologic phenotype, 10 lesions (13.9%) were associated with multicentric cancers (Table 5). Moreover, 9 of those 10 lesions were early cancers. The proportion of multicentric cancer among early papillary cancers was exceedingly high (9/24: 37.5%). Therefore, in the case of papillary adenocarcinoma, especially with early cancers, careful follow-up is necessary after initial surgery for early detection of metachronous cancer. Long-term follow-up is also important because many metachronous cancers developed 5–10 years after the initial surgery.

It is also noteworthy that most of the multicentric cancers were associated with superficial epithelial tumor spread and extensive dysplastic epithelium around the tumor (Tables 1 and 2 and Fig. 2). Rougemont et al. (13) recently reported a case of multifocal early intrahepatic cholangiocellular carcinoma in extensive biliary dysplasia. Extensive dysplasia in the background biliary epithelium suggests that multicentric adenocarcinomas might arise from the carcinogenetic background epithelial dysplasia. These multicentric cancer cases were consistent with the proposition by Nakanuma and Zen in which cholangiocellular carcinomas develop with a multistep progression from low-grade biliary intraepithelial dysplasia to high-grade dysplasia and carcinoma *in situ* (14–16). Hyperplasia–dysplasia–carcinoma sequence in a multistep carcinogenesis of the biliary tract has been proposed (6,9,13–17). Therefore, multicentric adenocarcinoma of the biliary tract can be used to investigate morphological and genetic alterations in carcinogenesis.

Table 5. Comparison of clinicopathological characteristics of papillary adenocarcinoma between multicentric and single cancers (the number of papillary adenocarcinoma lesions was 10 in multicentric cases and 62 in single cases)

	Multicentric lesions ($n = 10$)	Single lesions ($n = 62$)	P value
Early cancers	9	15	<0.001
Lymph node metastasis	0	18	0.047
R0 resection	10	52	0.20
Recurrence			
Remnant bile duct	2	0	0.017
Local	0	2	0.74
Lymph node	0	7	0.34
Peritoneum	0	5	0.47
Distant organ	0	16	0.07

Long-term outcomes of multicentric cancers were also very unique. It is remarkable that only one patient with multicentric adenocarcinoma died from cancer progression, although overall survival was not statistically different between multicentric cases and single cases ($P = 0.47$). Long-term survival can be expected after surgery in patients with multicentric biliary adenocarcinoma. Considering recurrence, it should be noted that remnant bile duct recurrence developed in a patient with synchronous multicentric cancer despite R0 resection (Table 1, Case #6). This recurrence might be considered to be metachronous tertiary cancer even though it developed within 2 years after the prior surgery. Surgical indications for metachronous lesions can be the same as for single lesions because multicentric cancers are likely to be early cancers without lymph node metastasis. Previous reports have demonstrated initial experiences of safety after aggressive repeated resection for metachronous cancer of the biliary tract (6–8,18,19). Repeated resection for metachronous lesions might improve survival of those patients. However, reoperation is technically demanding because initial surgery is likely to be pancreaticoduodenectomy or major hepatectomy with biliary reconstruction. In this analysis, one patient (Table 2, Case #3) died after the repeated resection because of post-operative liver failure. Liver function reserve should be critically examined before reoperation, especially after initial hepatectomy. Careful perioperative management is essential for reoperations. Further case accumulation is necessary to clarify the safety and efficacy of repeated resection for metachronous cancer.

A main limitation of this analysis was that it was a single institutional study and the number of cases could be larger. Further observation is necessary to draw a firm conclusion, especially regarding the safety and effectiveness of aggressive repeated resection for metachronous lesions of the remnant bile duct.

In conclusion, the present study has several important findings regarding the distinct features of multicentric adenocarcinoma of the biliary tract:

Pathologically, multicentric adenocarcinoma is more likely to be early cancer and papillary carcinoma with superficial epithelial tumor spread and extensive dysplastic epithelium, but less likely to have lymph node metastasis.

Multicentric adenocarcinomas can develop remnant bile duct recurrence (or tertiary cancer) despite R0 resection.

Thirty-seven percent of early papillary adenocarcinomas were associated with multicentric cancer. Close and long-term follow-up of patients with multicentric cancer and early papillary cancer is very important for early detection of metachronous lesions.

Since multicentric cancer is likely to be early cancer without lymph node metastasis, aggressive repeated resection of the metachronous lesions might improve survival of patients with multicentric adenocarcinoma of the biliary tract. Careful perioperative management is essential for reoperations.

Conflict of interest statement

None declared.

References

1. Hori H, Ajiki T, Fujita T, Okazaki T, Suzuki Y, Kuroda Y, et al. Double cancer of gall bladder and bile duct not associated with anomalous junction of the pancreaticobiliary duct system. *Jpn J Clin Oncol* 2006;36:638–42.
2. Fujii T, Kaneko T, Sugimoto H, Okochi O, Inoue S, Takeda S, et al. Metachronous double cancer of the gallbladder and common bile duct. *J Hepatobiliary Pancreat Surg* 2004;11:280–5.
3. Okamura K, Hayakawa H, Kuze M, Takahashi H, Kosaka A, Mizumoto R, et al. Triple carcinomas of the biliary tract associated with congenital choledochal dilatation and pancreaticobiliary maljunction. *J Gastroenterol* 2000;35:465–71.
4. Kasuya K, Nagakawa Y, Matsudo T, Ozawa T, Tsuchida A, Aoki T, et al. p53 gene mutation and p53 protein overexpression in a patient with simultaneous double cancer of the gallbladder and bile duct associated with pancreaticobiliary maljunction. *J Hepatobiliary Pancreat Surg* 2009;16:376–81.
5. Hasumi A, Matsui H, Suigoka A, Uyama I, Komori Y, Fujita J, et al. Precancerous conditions of biliary tract cancer in patients with pancreaticobiliary maljunction: reappraisal of nationwide survey in Japan. *J Hepatobiliary Pancreat Surg* 2000;7:551–5.
6. Hibi T, Sakamoto Y, Tochigi N, Ojima H, Shimada K, Sano T, et al. Extended right hemihepatectomy as a salvage operation for recurrent bile duct cancer 3 years after pancreatoduodenectomy. *Jpn J Clin Oncol* 2006;36:176–9.
7. Todoroki T, Fukuda Y, Kawamoto T, Saida Y, Ohara K, Iwasaki Y, et al. Long-term survivors after salvage surgery combined with radiotherapy for recurrence of stage IV main hepatic duct cancer—report of two cases. *Hepatogastroenterology* 1993;40:285–93.
8. Lees CD, Zapolanski A, Cooperman AM, Hermann RE. Carcinoma of the bile ducts. *Surg Gynecol Obstet* 1980;151:193–8.
9. Kurata M, Okamoto A, Suzuki T, Matsumoto G, Tsuruta K, Honda G, et al. Metachronous carcinomas of the biliary tract in a patient treated three times with curative surgery. *Case Rep Gastroenterol* 2009;3:84–91.
10. Okamoto A, Tsuruta K, Matsumoto G, Takahashi T, Kamisawa T, Egawa N, et al. Papillary carcinoma of the extrahepatic bile duct: characteristic features and implications in surgical treatment. *J Am Coll Surg* 2003;196:394–401.
11. Japanese Society of Biliary Surgery. *Classification of Biliary Tract Carcinoma*. 2nd edn. Tokyo: Kanehara and Co., Ltd. 2004.
12. International Union Against Cancer. *TNM Classification of Malignant Tumours*. 7th edn. Hoboken, NJ: Wiley-Blackwell 2009.
13. Rougemont AL, Genevay M, McKee TA, Gremaud M, Mentha G, Rubbia-Brandt L. Extensive biliary intraepithelial neoplasia (BilIN) and multifocal early intrahepatic cholangiocarcinoma in non-biliary cirrhosis. *Virchows Arch* 2010;456:711–7.
14. Shimonishi T, Sasaki M, Naknuma Y. Precancerous lesions of intrahepatic cholangiocarcinoma. *J Hepatobiliary Pancreat Surg* 2000;7:542–50.
15. Zen Y, Sasaki M, Fujii T, Chen TC, Chen MF, Yeh TS, et al. Different expression patterns of mucin core proteins and cytokeratins during intrahepatic cholangiocarcinogenesis from biliary intraepithelial neoplasia and intraductal papillary neoplasm of the bile duct—an immunohistochemical study of 110 cases of hepatolithiasis. *J Hepatol* 2006;44:350–8.
16. Nakanuma Y, Sasaki M, Sato Y, Ren X, Ikeda H, Harada K. Multistep carcinogenesis of perihilar cholangiocarcinoma arising in the intrahepatic large bile ducts. *World J Hepatol* 2009;1:35–42.
17. Suzuki M, Takahashi T, Ouchi K, Matsuno S. The development and extension of hepatobiliary bile duct carcinoma: a three-dimensional tumor mapping in the intrahepatic biliary tree visualized with the aid of a graphics computer system. *Cancer* 1989;64:658–66.
18. Jang JY, Kim SW, Park DJ, Ahn YF, Yoon YS, Choi MG, et al. Actual long-term outcome of extrahepatic bile duct cancer after surgical resection. *Ann Surg* 2005;241:77–84.
19. Targarona EM, Zografos G, Habib NA. Liver resection for recurrent hilar cholangiocarcinoma. *Br J Surg* 1993;80:1433.

J Hepatobiliary Pancreat Sci (2011) 18:567–574
DOI 10.1007/s00534-011-0371-z

ORIGINAL ARTICLE

Borderline resectable pancreatic cancer: rationale for multidisciplinary treatment

Shinichiro Takahashi · Taira Kinoshita · Masaru Konishi · Naoto Gotohda · Yuichiro Kato · Takahiro Kinoshita · Tatsushi Kobayashi · Syuichi Mitsunaga · Kohei Nakachi · Masafumi Ikeda

Published online: 18 February 2011

Abstract
Background Borderline resectable pancreatic cancer (BRPC) appears to be most frequently related to a positive surgical margin and has a poor prognosis after resection. However, few reports are available on differences in tumor characteristics and prognoses among resectable pancreatic cancer (PC), BRPC, and unresectable PC.
Methods Records of 133 patients resected for pancreatic ductal adenocarcinoma and 185 patients treated as locally advanced PC (LAPC) were reviewed.
Results Twenty-four patients who initially underwent resection (BRPC-s) and 10 patients who were initially treated as LAPC (BRPC-n) met the criteria for BRPC. Prognosis of BRPC was significantly better than that of unresectable PC, but was significantly worse than that of resectable PC. BRPC-s showed more frequent nerve plexus invasion ($P < 0.01$), portal vein invasion ($P < 0.01$), and loco-regional recurrence ($P = 0.03$) than resectable PC. The positive surgical margin rate was not significantly higher in BRPC-s (29%) than in resectable PC (19%) ($P = 0.41$).
Conclusions BRPC had a poorer prognosis with more local failure than resectable PC although prognosis of BRPC was significantly better than that of unresectable PC. Considering the tumor and treatment characteristics, multidisciplinary treatment including resection is required for BRPC.

Keywords Pancreatic cancer · Resection · Borderline resectable pancreatic cancer

S. Takahashi (✉) · T. Kinoshita · M. Konishi · N. Gotohda · Y. Kato · T. Kinoshita
Department of Hepatobiliary Pancreatic Surgery, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan
e-mail: shtakaha@east.ncc.go.jp

T. Kobayashi
Department of Diagnostic Radiology, National Cancer Center Hospital East, Chiba, Japan

S. Mitsunaga · K. Nakachi · M. Ikeda
Department of Hepatobiliary Pancreatic Oncology, National Cancer Center Hospital East, Chiba, Japan

Introduction

Borderline resectable pancreatic cancer (BRPC) is a newly proposed category that is now being established [1–4]. BRPC tumors can be understood radiologically and technically as an intermediate stage between resectable tumor and locally advanced tumor. These tumors are often treated as resectable in some specialized centers, but are more likely to be removed with positive surgical margins, with positive margins generally being predictive of decreased survival [5, 6]. Multidisciplinary treatment for BRPC aiming to improve surgical resectability and prognosis is thought to be a promising strategy [7]. The surgical oncology group of the MD Anderson Cancer Center proposed neoadjuvant chemotherapy and chemoradiation for BRPC patients, and they reported favorable outcomes, with a low positive surgical margin rate and relatively long survival after the combined modality treatment [1, 2]. In the report of the AHPBA/SSO/SSAT Consensus Conference, it was recommended that BRPC patients should be studied separately from those with resectable PC or unresectable PC [7].

However, little information is available on the differences in patient demographics and surgical results,

including prognosis and positive surgical margin rate, between resectable PC and BRPC that might support a rationale for selective neoadjuvant therapy for BRPC patients. Furthermore, prognosis of BRPC patients initially treated with nonsurgical treatment such as chemotherapy or chemoradiotherapy has not been well documented.

The objective of this paper was to investigate clinicopathological factors and prognosis in patients with resected BRPC and to compare the above factors between patients with resected BRPC and those with resectable PC. We also compared outcomes between BRPC and unresectable PC to assess prognostic significance of surgical resectability in PC patients initially treated with nonsurgical treatment for local development of the tumor.

Methods

Definition of BRPC

BRPC was defined in this study according to the criteria for resectability status in the "NCCN Practice Guidelines in Oncology" [4]. Namely, the criteria for BRPC were as follows: (1) severe superior mesenteric vein (SMV)/portal impingement; (2) <180° tumor abutment on the superior mesenteric artery (SMA); (3) abutment or encasement of the hepatic artery, if reconstructible; and (4) SMV occlusion, if of a short segment, and reconstructible. In this study, in terms of SMV/portal impingement, only patients with bilateral SMV/portal impingement were included.

Patient population

A total of 133 patients who had undergone surgical resection for pancreatic ductal adenocarcinoma at the National Cancer Center Hospital East between January 2002 and December 2008 were examined retrospectively. No patients received neoadjuvant chemotherapy or chemoradiation. According to staging by multidetector-row computed tomography (MDCT) findings, 24 patients met the criteria for BRPC, and the remaining 109 patients had resectable pancreatic cancer. The 24 BRPC patients who were initially treated with resection were classified as BRPC-s.

In order to find BRPC patients who had been initially treated with nonsurgical therapy, resectability status of a total of 185 patients who were treated as locally advanced pancreatic cancer (LAPC) between January 2002 and December 2008 was examined. According to staging by MDCT findings, 10 patients met the criteria for BRPC, and the remaining 175 patients had unresectable pancreatic cancer. The 10 BRPC patients who were initially treated with nonsurgical therapy were classified as BRPC-n. For treatment of the 10 BRPC-n patients, chemotherapy was performed in 7 and concurrent or sequential chemoradiotherapy in 3. For treatment of the 175 unresectable PC patients, chemotherapy was performed in 120 patients, radiotherapy in 2, and concurrent or sequential chemoradiotherapy in 53. After initial therapy, surgical resection was performed in 2 patients out of the 10 BRPC-n patients, and 3 out of the 175 unresectable patients.

All patients had a confirmed pathological diagnosis as pancreatic ductal adenocarcinoma.

Operative procedure

Patients with ductal adenocarcinoma of the head of the pancreas typically underwent subtotal stomach-preserving pancreaticoduodenectomy, and those with ductal adenocarcinoma of the body or tail underwent distal pancreatectomy. All patients underwent dissection of lymph nodes, including nodes along the common hepatic artery (CHA) and SMA and the regional lymph nodes around the pancreas, while patients with pancreatic head cancer underwent dissection of the lymph nodes in the hepatoduodenal ligament in addition. Dissection of para-aortic lymph nodes was not routinely performed. The operative procedure generally included resection of the nerve plexus around the SMA (half on the tumor side), the nerve plexus around the CHA, and the celiac plexus. When the portal vein (PV) or SMV was involved, PV/SMV resection was performed if reconstructible. However, when the SMA, CHA, or celiac axis was definitively involved at operation, the tumor was considered unresectable, unless distal pancreatectomy with celiac axis resection for pancreatic body cancer that involved the celiac axis or the proximal part of the CHA could be performed for curative intent. Intraoperative pathological assessment of the pancreatic cut end margin was performed using frozen tissue sections. If the cut end margin was positive for adenocarcinoma, further resection of the pancreas was performed.

CT examination

All images were viewed on soft-tissue windows of MDCT. Two-phase abdominal contrast-enhanced CT (arterial and portal venous phase) was performed with 16-slice MDCT scanner in all patients before initial treatment. Images were reconstructed at 2-mm intervals using a standard soft-tissue algorithm. For interpretation of CT images, axial images were mainly assessed, but oblique-coronal MPR images

were assessed concurrently whenever available. All interpretations in terms of resectability were made by experienced surgeons and a radiologist according to the aforementioned criteria for BRPC.

Pathology investigations

Each resected pancreatic specimen was examined histologically for the histological type, tumor size, arterial invasion, PV invasion, nerve plexus invasion, bile duct invasion, duodenal invasion, serosal invasion, retroperitoneal invasion, nodal status, and margin status. Histological diagnosis was performed according to the TNM classification system of malignant tumors published by the International Union Against Cancer (UICC), 6th edition [8].

Postoperative adjuvant chemotherapy

No patients received postoperative adjuvant chemotherapy until 2007. Since 2007, 35 patients have received adjuvant chemotherapy consisting of three weekly intravenous infusions of gemcitabine 1,000 mg/m^2 followed by a 1-week pause for 6 months. Alternatively, 80 mg/m^2 of oral S-1 was given for 4 weeks, followed by a 2-week pause, for 6 months in 10 patients on a protocol designed for patients after resection of pancreatic adenocarcinoma.

Survival

Patients were followed regularly at 3-month intervals with blood testing and MDCT. Survival and follow-up were calculated from the time of the operation to the date of death or last available follow-up, and for LAPC patients, from the time of beginning first treatment. Cause of death and recurrence status were recorded. The survivors' median follow-up time after surgery was 26.4 months.

Statistical analysis

The χ^2 test and Student t test were used for univariate comparisons of clinicopathological factors except preoperative CA 19-9 level between subgroups based on resectability status. Mann-Whitney's U test was used to compare preoperative CA 19-9 level between subgroups. Analyses of survival were performed using the Kaplan–Meier method [9], and differences between the curves were tested using the log-rank test. Factors related to survival were analyzed with the Cox proportional hazards regression model [10]. A P value of <0.05 was considered significant. Statistical analysis was performed using SPSS version 17.0 software (SPSS, Chicago, IL, USA).

Results

MDCT findings for BRPC

During the period of this study, 24 of the 133 patients who initially underwent surgical resection for pancreatic ductal adenocarcinoma (i.e., BRPC-s) and 10 of the 185 patients who were initially treated as LAPC (i.e., BRPC-n) met the criteria for BRPC. Bilateral SMV/portal impingement was recognized in 11 patients (Fig. 1a, b), tumor abutment on the CHA in 7 (Fig. 1c), tumor abutment on the SMA in 16 (Fig. 1d), and tumor abutment on the celiac axis in 7.

Clinicopathological features of patients with BRPC

Table 1 summarizes the clinicopathological features of patients with resectable PC, BRPC, and unresectable PC. Tumor located in the head of the pancreas was significantly more frequent in patients with resectable PC than in those with BRPC ($P < 0.01$). Tumor size of BRPC was significantly greater than that of resectable PC ($P < 0.01$) and was significantly smaller than that of unresectable PC ($P < 0.01$). Preoperative CA 19-9 value seemed to increase as tumor resectability status progressed, but the differences were not significant.

Moreover, detailed pathological analyses were performed between resectable PC and BRPC-s. Tumor size of BRPC-s was 3.3 cm and tended to be greater than that of resectable PC ($P = 0.16$). Invasion of the artery, the PV, and the nerve plexus was seen in 14, 32, and 33 out of 109 resectable PC patients, and in 4, 14, and 18 out of 24 BRPC-s patients. Invasion of the PV and the nerve plexus was observed more frequently in BRPC-s than in resectable PC ($P < 0.01$). There was no significant difference in status of arterial invasion and invasion to other organs between the two subgroups. Patients with N1 were more frequently seen in BRPC-s patients ($n = 21$) than in resectable PC patients ($n = 81$), but the difference was not significant ($P = 0.19$). According to the TNM system [8], 1, 22, and 1 patients were diagnosed with stage IIA, IIB, and III disease, respectively, in BRPC-s patients, while 3, 25, 80, and 1 patients were diagnosed with IB, IIA, IIB, and III disease, respectively, in resectable PC patients.

Surgical resections of BRPC

In the BRPC-s group, subtotal stomach-preserving pancreaticoduodenectomy was performed in 15 patients, distal pancreatectomy in 4, distal pancreatectomy with celiac axis resection in 4, and total pancreatectomy in 1. In the 24 BRPC-s patients, 14 underwent SMV/PV resection, and 4 underwent celiac axis/CHA resection without reconstruction. The colon, jejunum, left adrenal gland, and left kidney