Multimodality Treatment of Pancreatic Cancer With Liver Metastases Using Chemotherapy, Radiation Therapy, and/or Chinese Herbal Medicine

Huaqiang Ouyang, MD,† Peng Wang, MD,*† Zhiqiang Meng, MD,*† Zhen Chen, MD,*† Er'xin Yu, MD,*† Huan Jin, PhD,‡ David Z. Chang, MD, PhD,§ Zhongxing Liao, MD,|| Lorenzo Cohen, PhD,¶ and Luming Liu, MD*†*

Objective: To explore the utility of multidisciplinary approaches in the treatment of patients with pancreatic cancer with liver metastases (PCLM).

Methods: From 2002 to 2007, a total of 164 consecutive patients with PCLM treated with chemotherapy, radiation therapy, and/or Chinese herbal medicine were included in this study. Clinical parameters, treatments received, and survival time from initial diagnosis were analyzed.

Results: Of the 164 patients, 113 (69%) were men and 51 (31%) were women, with median age of 58 years. One hundred thirty-two patients (80%) had synchronous liver metastases, and 57 patients (35%) had extrahepatic metastases. Overall median survival time of the 164 patients was 4.7 months; 23 (14%) were alive at least 12 months after initial diagnosis of liver metastases. Karnofsky performance status of less than 80, weight loss (>10% within 6 months), ascites, and carbohydrate antigen 19–9 of 1000 U/mL or greater were the most relevant predictors of poor survival. Multivariate analysis showed that chemotherapy and Chinese herbal medicine were protective factors.

Conclusions: Multimodality treatment is well tolerated by patients with PCLM and may be effective in prolonging their survival. Awareness of the implications of these prognostic factors may assist in evaluating the survival potential of patients and selecting the most appropriate treatments.

Key Words: pancreatic cancer, liver metastases, multimodality treatment, prognosis

(*Pancreas* 2011;40: 120–125)

Liver metastasis is a common feature of pancreatic adenocarcinomas. More than 50% of patients with pancreatic cancer have liver metastases at the time of diagnosis and is associated with a poor prognosis.[1,2] For patients with resectable disease, surgery is the treatment of choice, and it has been moderately effective, with 5-year survival rates ranging from 20% to 25%.[3–6] However, the median survival time for patients with pancreatic cancer liver metastases has been reported to be less than 6 months, regardless of whether the patients were treated with hepatic resection or palliative bypass procedures alone.[7–10]

Liver metastases are not resectable in most cases. The treatment aims for this population are to prolong survival and to maintain a good quality of life by controlling disease-related symptoms. Chemotherapy and radiation therapy have each been widely used to elicit such outcomes in locally advanced pancreatic carcinoma,[11,12] but these treatment modalities have been shown to have only limited effectiveness in patients with metastatic pancreatic carcinoma.[13] Recently, bevacizumab, a recombinant humanized anti–vascular endothelial growth factor monoclonal antibody, has gained considerable interest as a potentially effective chemotherapeutic agent for advanced pancreatic cancer and has been evaluated in combination with standard gemcitabine infusion in both phases 2 and 3 clinical trials.[14,15] However, the positive results of those early investigations were not reproduced in a subsequent study with a larger patient sample.[16]

Although multimodality treatments for resectable pancreatic cancer have gained favor in recent years, few reports on multidisciplinary treatments for pancreatic cancer with liver metastases (PCLM) have been published in the last decade.[17] Some of these studies indicate that a small subgroup of patients with PCLM may prolong their survival by undergoing surgical resection along with chemoradiation and that long-term survival may be possible in some cases.[18–21] In the future, the role of combined-modality therapy for metastatic pancreatic carcinoma should become more clear as many ongoing large trials begin to generate results.[22] The aim of the present study was to review our own 5-year experience using multimodality approaches in the management of unresectable PCLM to identify prognostic factors that may influence survival and to help identify which patients may benefit from these comprehensive treatment strategies.

MATERIALS AND METHODS

After receiving approval from the institutional review board of Fudan University Cancer Hospital, we retrospectively selected 243 consecutive patients with PCLM who were treated using a multimodality approach at the Fudan University Cancer Hospital in Shanghai, China, from January, 2002 to December, 2007. Pancreatic cancer and liver metastases had been diagnosed by open surgery biopsy (12/164, 7.3%) and fine-needle aspiration biopsy of the tumors (pancreatic tumor, 17.7%; liver metastases, 75%). We derived patient data from a review of inpatient and

From the *Department of Integrative Oncology and †Comprehensive Treatment Group for Hepatobiliary and Pancreatic Oncology, Cancer Hospital; and ‡Department of Biostatistics and Social Medicine, School of Public Health, Fudan University, Shanghai, China; and Departments of §Gastrointestinal Medical Oncology and ||Radiation Oncology and ¶Integrative Medicine Program and Departments of Behavioral Science and General Oncology, University of Texas M. D. Anderson Cancer Center, Houston, TX.

Received for publication January 1, 2010; accepted May 7, 2010.

Reprints: Luming Liu, MD, Department of Integrative Oncology, Cancer Hospital, Fudan University, 270 Dong An Rd, 200032 Shanghai, China (e-mail: llm1010@yahoo.com.cn).

Drs Ouyang and Wang contributed equally to the work.

This study was supported in part by the National Cancer Institute, U.S.A. R21 CA108084 and U19 CA121503; by the Ministry of Science and Technology, P. R. China 2005DFA30130; by the "Climbing Up" Project of Shanghai Municipal Commission for Science and Technology, no. 064307053; by Shanghai Nature Science Fund no. 09ZR1406800; and by Shanghai Municipal Health Bureau no. 2006YSB008, Shanghai, P. R. China. These funding sources had no influence on the decision to submit the manuscript for publication or the writing of the report.

outpatient medical records and from direct patient follow-up visits. All eligible patients were presented to a multidisciplinary hepatobiliary and pancreatic cancer treatment group for therapeutic recommendations. Written informed consent was obtained from patients before treatment. Patients with neuroendocrine tumors or incomplete pathological reports were excluded from the current analysis, leaving 164 in the study group.

Of the 164 patients with PCLM, 113 (69%) were men and 51 (31%) were women. The median age was 58 years (range, 15–81 years). Only 2 patients received liver wedge resection along with distal pancreatectomy because either pancreatic tumor or single liver metastasis could be totally resected. Forty-three (26%) underwent transcatheter arterial infusion (TAI), and 90 (55%) underwent transcatheter arterial chemoembolization (TACE). The use of TAI or TACE was at the discretion of the referring physician. Systemic chemotherapy (SCT) was applicable to patients with better expected survival and who refused TACE treatment. Fifty-six patients (34%) received SCT according to the gemcitabine-based regimens used at the time. External-beam radiation therapy (EBRT) at doses ranging from 40 to 60 Gy (median, 50 Gy) was used to treat pancreatic carcinomas and was administered to 91 patients (55%) (age <70 years). A high-intensity focused ultrasound (HIFU) system (Chongqing HIFU; Chongqing, China) was used to treat 9 patients' pancreatic tumors (located mainly in pancreatic body and tail) under the guidance of real-time ultrasonography. In addition, QYHJ decoction was recommended for all patients, which is composed of Chinese herbs (spreading Hedyotis herb, barbed skullcap herb, Ma-yuen Job's tears seed, Lucid Ganoderma, and Chinese hawthorn fruit), as a complementary treatment. The QYHJ decoction was obtained in precompounded form by prescription. Each course of treatment consisted of 1 oral dose per day in decoction form for 14 days, with 122 patients (74%) receiving a median of 8 courses (range, 2–82 courses).

Statistical Analysis

Overall survival from the date of definitive diagnosis of liver metastases from pancreatic cancer was estimated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. The continuous variables were divided into categories using population quartiles, upper normal values, and published data to determine cutoff values. Multivariate analysis was performed using the Cox proportional hazards model; this analysis was used to test the influence of all prognostic indexes (PIs) analyzed by univariate analysis (regardless of significance). $P < 0.05$ was considered statistically significant. With the significant prognostic variables obtained from the multivariate analysis, we calculated the relative risk of death (RRD) for each patient using the following formula:

$$h(t)/h_0(t) = \exp(\beta_1 X_1 + \beta_2 X_2 + ... + \beta_k X_k),$$

where $h(t)$ is the hazard rate for survival of a particular patient at time t, $h_0(t)$ is the hazard computed at the average values of the variables in the model, β_1 to β_k are the regression coefficients of the variables, and X_1 to X_k are the values of the variables for a particular patient.[23] Higher values of RRD indicate a worse prognosis, and lower values a better prognosis.

All statistical analyses were performed using STATA software (version 10.0; College Station, Tex).

RESULTS

A total of 453 patients with locally advanced and metastatic pancreatic cancer presented to Fudan University Cancer Hospital over a 5-year period from 2002 to 2007. Of these patients, 243 (53.6%) were found to have liver metastases at the time of initial presentation, and 164 (36%) had histological evidence of adenocarcinoma. Demographic and clinical characteristics for these 164 patients are summarized in Table 1.

Treatment Outcomes

At a median follow-up period of 13 months (range, 6–68 months), overall 1-, 3-, and 5-year survival rates for the 164 patients in the study population/group were 18.3%, 8.8%,

TABLE 1. Demographic and Clinical Characteristics of 164 Patients With PCLM

	n	Median Survival, mo	1-y Survival Rate, %	Univariate *P*
Sex				0.131
Male	113	4.5	16.2	
Female	51	6.2	23.1	
Age, y				**0.034**
≤55	66	5.4	22.1	
>55	98	4.5	15.3	
KPS				**<0.001**
<80	44	2.9	4.6	
80–100	120	5.6	23.5	
Primary tumor localization				0.602
Head	65	5.1	21.3	
Body and tail	99	4.7	16.3	
Onset of liver metastases				0.886
Synchronous	132	4.9	18.0	
Metachronous	32	3.8	19.4	
Primary tumor resection				0.163
Resected	24	4.2	28.1	
Intact	140	4.7	16.6	
Site of liver disease				0.167
Unilobar	53	5.7	24.0	
Bilobar	111	4.5	15.6	
Extent of liver involvement				0.428
≤50%	119	4.8	19.0	
>50%	45	4.7	16.1	
Extrahepatic metastases				0.520
No	107	4.5	17.7	
Yes	57	5.3	19.9	
Site of extrahepatic metastases				0.232
Lung	15	7.6	31.6	
Spleen	15	5.4	12.0	
Bone	10	4.7	20.0	
Regional lymph node swelling				0.366
No	119	5.0	20.3	
Yes	45	4.4	12.7	
Symptoms				
Pain	122	4.5	12.9	**0.003**
Weight loss	105	4.2	7.6	**0.002**
Epigastric discomfort	91	4.7	17.4	0.701
Anorexia	76	4.1	14.7	**0.006**
Nausea and vomiting	24	3.7	20.8	**0.003**
Ascites	13	2.6	0	**<0.001**

P value in bold font are statistically significant.

and 7.0%, respectively, and median survival time was 4.7 months (range, 0.5–67.6 months) (Fig. 1). Of these patients, 23 survived for 1 year, 6 for 3 years, and 1 for 5 years. At the time of analysis, 21 patients (12.8%) were still alive. Three patients who attained stable disease were lost to follow-up during or soon after treatment period. These patients with stable disease were considered still alive at last follow-up and were censored thereafter.

Toxicity and Complications

Gemcitabine-based chemotherapy (including TAI/TACE) was well tolerated. Of the 153 patients who received chemotherapy, grade 4 leukocytopenia and thrombocytopenia occurred in 17 (11.1%) and 9 (5.9%) patients, respectively, but both were generally brief and reversible. Most patients experienced some degree of postembolization syndrome in the TACE group, which generally lasted 48 to 72 hours. Elevated alanine aminotransferase and aspartate aminotransferase levels were frequent nonhematologic adverse effects. Grade 4 toxicities were observed as elevated alanine aminotransferase levels in 17 patients (18.9%) of the TACE group (n = 90); these toxicities returned to normal within 3 weeks. Seven patients developed grade 4 total bilirubin elevation during treatment of EBRT, one of whom died of hepatic encephalopathy, others recovered to the initial levels within a month. No skin burns caused directly by HIFU were observed, and no adverse effects and toxicities were seen in 122 patients (74.4%) during treatment of Chinese herbal medicine (CHM).

Univariate Analysis

Univariate analysis revealed that age older than 55 years, Karnofsky performance status (KPS) of less than 80, pain, weight loss (>10% within 6 months), ascites, anorexia, and nausea and vomiting were significantly associated with reduced median survival (Table 1). Most patients had abnormal liver function tests at initial assessment. The most common abnormality was elevated γ-glutamyltranspeptidase (63.4%) and serum alkaline phosphatase (48.1%). Serum tumor markers such as carbohydrate antigen (CA) 19-9, which was collected from patients without obstructive jaundice or in the presence of successfully drained obstructive jaundice, were significantly higher (≥1000 U/mL) in 84 patients (54.3%), followed by elevated carcinoembryonic antigen (49.4%). Abnormal liver function findings or markedly elevated serum tumor markers were correlated with a poor prognosis. Subsequent TACE, SCT, and CHM were considered protective factors on univariate analysis (Table 2).

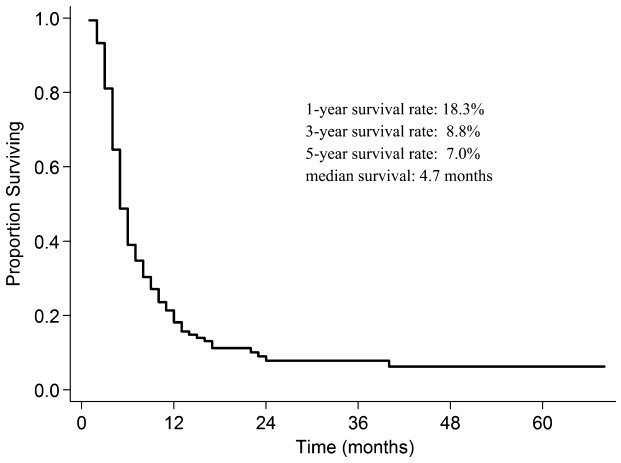

FIGURE 1. Overall survival of 164 pancreatic cancer patients with liver metastases.

TABLE 2. Simultaneous Treatment of Primary Tumor and Hepatic Metastases

	n	Median Survival, mo	1-y Survival Rate, %	*P*
Primary site				
Distal pancreatectomy	2	7.1	0	—
Conformal radiotherapy				0.187
No	73	4.3	14.3	
Yes	91	5.1	19.8	
HIFU				0.466
No	155	4.7	17.7	
Yes	9	7.9	11.1	
Liver metastases				
Wedge resection	2	7.1	0	—
TAI/TACE				
1	83	4.2	9.7	
2	35	6.0	18.4	
≥3	15	12.3	50.4	**<0.0001**
SCT				**0.005**
No	108	4.4	13.2	
Yes	56	5.7	25.7	
CHM				**<0.001**
No	42	3.9	4.8	
Yes	122	5.4	21.9	

P value in bold font are statistically significant.

Multivariate Analysis

Patient-related, tumor-related, and treatment-related variables that were found to be significantly associated with overall survival by univariate analysis were subsequently evaluated by Cox regression analysis to determine independent risk factors for survival in PCLM. Pain, weight loss (>10% within 6 months), ascites, elevated γ-glutamyltranspeptidase (≥54 IU/L), and elevated CA19-9 (≥1000 U/mL) were found to be independent predictors of poor survival; chemotherapy (including TACE) and CHM were found to be independent protective factors (Table 3; Fig. 2). Regression coefficients used in calculating RRD are shown in Table 3.

Prognostic Index Calculation and Stratification Into 4 Treatment Outcome Groups

Relative risk of death was calculated for each patient using the following equation: $h(t)/h_0(t) = \exp(\text{KPS} \times 0.812 + \text{weight loss} \times 0.589 + \text{ascites} \times 1.657 + \text{CA19-9} \times 0.689 - \text{chemotherapy} \times 0.712 - \text{CHM} \times 0.666)$. Because the PI was expressed as $h(t)/h_0(t)$, where $h(t)/h_0(t)$ was the RRD for a given patient, and using $X_1, X_2, \ldots X_6$ to represent the clinical variables (Table 3), the equation can be rewritten as follows:

$$\text{PI} = 0.812X_1 + 0.589X_2 + 1.657X_3 + 0.689X_4 + 0.711X_5 - 0.666X_6.$$

All variables were introduced as dichotomous variables (present = 1, absent = 0). The median PI value was −0.221 (range, −1.377 to 3.747); higher PI values indicated a worse prognosis. Using the PI values, we could stratify our study population into 4 groups with significantly different survival times ($P < 0.05$): "low-risk" group, PI of less than −0.5 (30 patients); "moderate-risk" group, PI of −0.5 to 0 (52 patients); "high-risk"

TABLE 3. Multivariate Prognostic Analysis of 164 Patients With PCLM

	Variable	Category	Coefficient	SE	*P*	95% CI
X_1	KPS	≥80 vs <80	0.812	0.241	0.001	0.339–1.285
X_2	Weight loss	No vs yes	0.589	0.225	0.009	0.149–1.03
X_3	Ascites	No vs yes	1.657	0.413	<0.001	0.847–2.467
X_4	CA19-9	<1000 vs ≥1000	0.689	0.22	0.002	0.257–1.121
X_5	Chemotherapy	No vs yes	−0.711	0.331	0.032	−1.36 to −0.061
X_6	CHM	No vs yes	−0.666	0.237	0.005	−1.13 to −0.202

group, PI of 0–0.5 (44 patients); and "extremely high-risk" group, PI of greater than 0.5 (33 patients) (Table 4; Fig. 3).

Patients Who Survived 12 Months or Greater

Of the 164 patients, 23 (14%) were alive at least 1 year after the diagnosis of PCLM. Of these 23 patients, 21 patients (91%) were administered CHM regularly, 12 (52%) underwent TACE twice, and 6 (26%) underwent TACE 3 times or more, which seemed to prolong their survival. Furthermore, 6 (3.7%) of the 164 patients were alive at least 3 years after PCLM diagnosis, and 1 patient was alive more than 5 years after the diagnosis. The median age of these long-term survivors was 57 years at diagnosis. Most of these patients had a low CA19-9 level, and 4 patients had weight loss (>10% within 6 months), but none had ascites.

Number of Treatments and Overall Survival

Because our aim was to analyze combined-modality approaches for treating PCLM, we explored the relationship between the number of treatments received and the overall survival rate throughout the follow-up period. Our results showed that the overall survival rate throughout the follow-up period was directly proportional to the number of treatment modalities received (Fig. 4).

DISCUSSION

Because the liver is the most frequent site of disease recurrence in patients with advanced pancreatic carcinoma, reducing the incidence of liver metastases may be an effective way of decreasing the likelihood of recurrence and thus improving the prognosis of these patients. Unfortunately, only a few studies focusing on the treatment of PCLM have been published. Most of these studies reported single-institution experiences with a wide variety of pancreatic tumor types distributed over a small number of patients.[8,9,24–27] For instance, during our review of the literature, we identified only 6 studies on PCLM treated by diverse treatment modalities that included more than 10 patients. To our knowledge, the current study is the largest study regarding PCLM performed to date and the first to investigate prognostic factors for multimodality treatment of this disease.

Pancreatic cancer with liver metastases has a poor prognosis, with a median survival of 6 months or less.[10] In the current study, median survival was 4.73 months, and the 1-year overall survival rate was 18.3%. These results are similar to, and in some cases, better than, the findings reported by previous studies. The improvement in our results over those of other researchers may be explained by the fact that our institution used a multimodality treatment for PCLM.

In the present study, we confirmed several prognostic variables previously identified in advanced pancreatic cancer, such as performance status, ascites, weight loss, and elevated CA19-9 levels.[9,28–32] In addition, we also evaluated the effects of treatments on prognosis.

Surgery, whether curative or palliative, is still considered a controversial treatment method for patients with PCLM.[33,34] Gleisner et al[8] reported the treatment outcome of 22 patients with PCLM who underwent simultaneous hepatic and pancreatic resection. In their analysis, the median size of the largest hepatic lesion was 0.6 cm, and in our study, it was 3.3 cm. Accordingly, in the study of Gleisner et al,[8] the median survival after diagnosis of liver metastasis was 5.9 months, whereas it was only 4.7 months in our study. However, the researchers concluded that "even in well-selected patients with low-volume metastatic liver disease, simultaneous resection of periampullary or pancreatic carcinoma with synchronous liver metastases did not result in long-term survival in the overwhelming majority of patients."[8] Recently, Müller et al[9] reported 136 cases of advanced pancreatic adenocarcinoma, 71 of which were PCLM, treated by

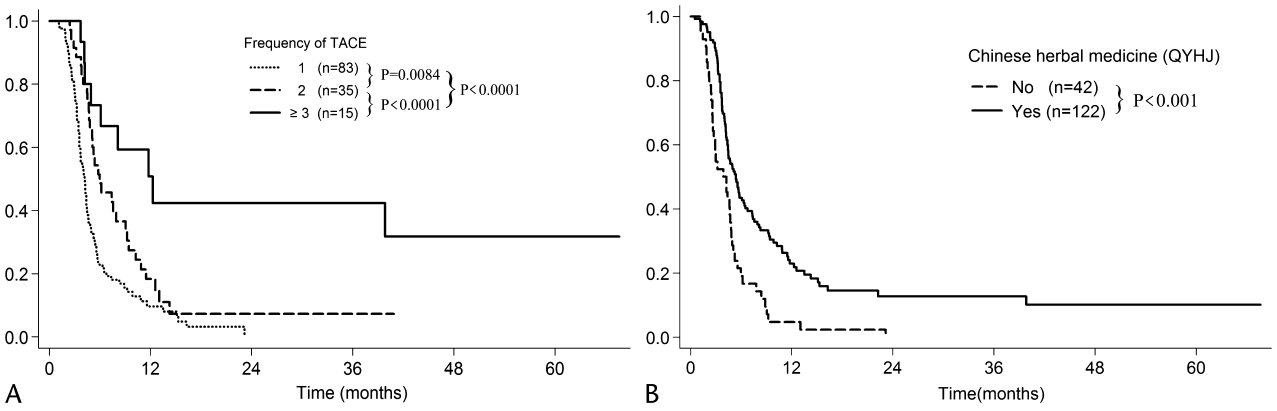

FIGURE 2. Cumulative survival among patients with pancreatic cancer liver metastases according to CHM and frequency of TACE.

TABLE 4. Survival Among 159 Patients With PCLM According to Prognostic Indexes

Group	PI	n	Median Survival, mo	Survival Rate Years, %			*P*
				0.5	1	3	
Low risk	PI < −0.5	30	12.6	73.3	55.4	38.8	**<0.001**
Moderate risk	−0.5 ≤ PI ≤ 0	52	5.6	44.2	15.9	0	
High risk	0 < PI ≤ 0.5	44	4.7	27.3	11.4	0	
Extremely high risk	PI > 0.5	33	2.9	9.1	0	0	

P value in bold font are statistically significant.

bypass procedures alone. Their multivariate analysis found that American Society of Anesthesiologists score, presence of liver metastasis, pain, CA19-9 level, and carcinoembryonic antigen level were independent predictors of poor survival. Although an aggressive treatment strategy, such as surgery, may prolong the survival of a select subgroup of these patients, its exact role in the treatment of PCLM requires further evaluation.

Patients who received gemcitabine-based chemotherapy benefited in this series, with a median survival of 5.7 months. However, it must be remembered that patients who received chemotherapy were a select group with better general performance and endurance capacity. Compared with the TACE group, the overall response rate of patients receiving SCT was obviously insignificant. However, we found that the efficacy of TACE was closely associated with the number of treatments received: no remarkable improvement in survival was observed in patients with PCLM who underwent TACE only once.

Because PCLM is an incurable disease, we used only palliative treatment modalities. External-beam radiation therapy of the primary tumor was combined with chemotherapy. In a recent study, Hazard et al[35] found that radiation therapy was associated with improved survival compared with cancer-directed surgery without radiation in 1267 patients with pancreatic adenocarcinoma. High-intensity focused ultrasound ablation is a noninvasive treatment modality for localized tumors. An ultrasound beam can be focused as it passes through soft tissue, which enables the use of an external ultrasound energy source to induce thermal ablation of a tumor at a depth through the intact skin.[36] Unfortunately, we did not find a significant difference in survival between patients treated with EBRT and HIFU, which might be partly due to our small sample population. They should be studied in randomized controlled trials.

It is noteworthy that CHM was determined an important prognostic factor in our analysis. Fu et al[37] previously reported that the QYHJ decoction can inhibit pancreatic cancer cells from proliferating, as well as reverse multidrug resistance expression, when administered in combination with gemcitabine, thereby inhibiting tumor growth both in vitro and in vivo. In our study, we calculated a median survival of 5.4 months and 1-year survival rate of 21.9% for the CHM group, compared with a median survival of 3.9 months and 1-year survival rate of 4.8% for the non-CHM group ($P < 0.001$) (Fig. 2).

In this study, the number of treatment approaches used was found to remarkably affect overall survival during the follow-up period. For instance, patients who were treated with 3 or more approaches (including chemotherapy, EBRT, CHM, and HIFU) had a longer median survival time than patients treated with 2 or only 1 approach (median survival, 6.0 vs 4.5 vs 2.7 months) ($P < 0.001$; Fig. 4). Patients in the group with 3 or more treatments had a 1-year survival rate of 26% compared with 10% for those in the 2-treatment group and 4% for those in the 1-treatment group. These findings are of particular interest and are worth of further study.

Certainly, there are several limitations to the present study. Although the clinical data were prospectively collected, the study and analysis are retrospective and therefore subject to an inherent selection bias. The patients with TACE had larger primary tumors and a greater number of hepatic lesions than the medically or surgically treated patients. This is likely because our therapeutic model calls for palliative management and usually recommends TACE for patients with unresectable PCLM. Moreover, CHM is a common complementary therapy in our department, but the course of treatment is always individualized to the patient determined by a given physician because procedural norms have not yet been established. Owing to the few and restricted formal protocols available at our institutions, some therapeutic schedules were individualized on an ad hoc basis. Therefore, caution is warranted when interpreting these results; a

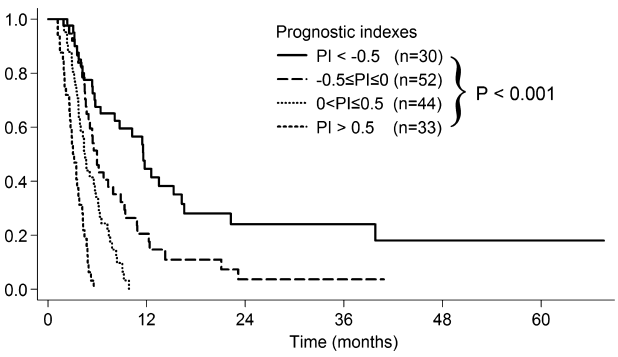

FIGURE 3. Survival among 159 patients with pancreatic cancer liver metastases according to PIs.

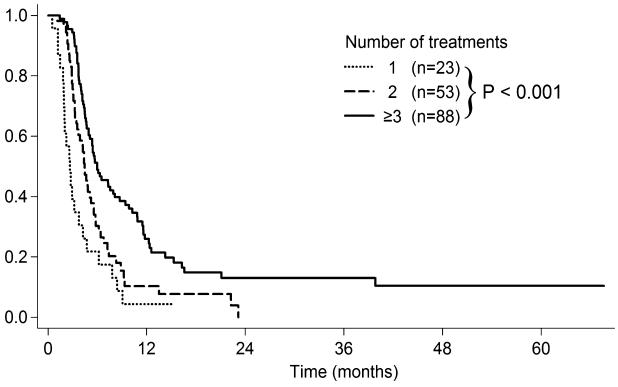

FIGURE 4. Survival among 164 patients with pancreatic cancer liver metastases according to the number of treatments received.

randomized controlled trial of multimodality treatments using these specific techniques is currently warranted.

In conclusion, to our knowledge, this is the first large study concerning the prognostic factors of patients with PCLM receiving multimodality treatment. Karnofsky performance status, weight loss, ascites, and elevated CA19-9 at diagnosis were independent factors indicating a poor prognosis. Chemotherapy and CHM were found to be protective factors. Overall, we conclude that multimodality treatment is well tolerated and may be effective in prolonging the survival of patients with PCLM.

REFERENCES

1. Hawes RH, Xiong Q, Waxman I, et al. A multispeciality approach to the diagnosis and management of pancreatic cancer. *Am J Gastroenterol*. 2000;95:17–31.
2. Meenk HG, Incrocci L, Kazemier G, et al. Adjuvant 5-FU based chemoradiotherapy for patients undergoing R-1/R-2 resections for pancreatic cancer. *Dig Surg*. 2005;22:321–328.
3. Parkin DM, Bray F, Ferlay J, et al. Estimating the world cancer burden: Globocan 2000. *Int J Cancer*. 2001;94:153–156.
4. Cameron JL, Riall TS, Coleman J, et al. One thousand consecutive pancreaticoduodenectomies. *Ann Surg*. 2006;144:10–15.
5. Winter JM, Cameron JL, Campbell KA, et al. 1423 Pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. *J Gastrointest Surg*. 2006;10:1199–1210; discussion 1210–1211.
6. Pawlik TM, Abdalla EK, Barnett CC, et al. Feasibility of a randomized trial of extended lymphadenectomy for pancreatic cancer. *Arch Surg*. 2005;140:584–589; discussion 589–591.
7. Schnall SF, Macdonald JS. Chemotherapy of adenocarcinoma of the pancreas. *Semin Oncol*. 1996;23:220–228.
8. Gleisner AL, Assumpcao L, Cameron JL, et al. Is resection of periampullary or pancreatic adenocarcinoma with synchronous hepatic metastasis justified? *Cancer*. 2007;110:2484–2492.
9. Müller MW, Friess H, Köninger J, et al. Factors influencing survival after bypass procedures in patients with advanced pancreatic adenocarcinomas. *Am J Surg*. 2008;195:221–228.
10. Jemal A, Siegel R, Ward E, et al. Cancer Statistics, 2008. *CA Cancer J Clin*. 2008;58:71–96.
11. Palmer KR, Kerr M, Knowles G, et al. Chemotherapy prolongs survival in inoperable pancreatic carcinoma. *Br J Surg*. 1994; 81:882–885.
12. Glimelius B, Hoffmann K, Sjoden P-O, et al. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol*. 1996;7:593–600.
13. Colucci G, Giuliani F, Gebbia V, et al. Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: a prospective, randomized phase III study of the Gruppo Oncologia dell'Italia Meridionale. *Cancer*. 2002;94:902–910.
14. Kindler HL, Friberg G, Singh DA, et al. Phase II trial of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer. *J Clin Oncol*. 2005;23:8033–8040.
15. Kindler HL, Niedzwiecki D, Hollis D, et al. A double-blind, placebo-controlled, randomized phase III trial of gemcitabine plus bevacizumab versus gemcitabine plus placebo in patients with advanced pancreatic cancer: a preliminary analysis of Cancer and Leukemia Group B. 2007 ASCO Annual Meeting Proceedings. *J Clin Oncol*. 2007;25:18S. Abstract 4508.
16. Gemcitabine plus bevacizumab no better than gemcitabine alone in clinical study of 600 patients with pancreatic cancer. *Cancer Biol Ther*. 2007;6:137.
17. Bilimoria KY, Bentrem DJ, Ko CY, et al. Multimodality therapy for pancreatic cancer in the U.S.: utilization, outcomes, and the effect of hospital volume. *Cancer*. 2007;110:1227–1234.
18. Berkson BM, Rubin DM, Berkson AJ. The long-term survival of a patient with pancreatic cancer with metastases to the liver after treatment with the intravenous alpha-lipoic acid/low-dose naltrexone protocol. *Integr Cancer Ther*. 2006;5:83–89.
19. Guillem P, Mornex F, Partensky C. Prolonged survival after resection of pancreatic cancer with a solitary hepatic metastasis. *Hepatogastroenterology*. 2004;51:603–605.
20. SuzukiY, Ku Y, Tominaga M, et al. Two-staged treatment with local resection and percutaneous isolated hepatic chemoperfusion for advanced pancreatic cancer with multiple liver metastases: report of a case. *Hepatogastroenterology*. 2001;48:574–577.
21. Ikeda M, Okada S, Tokuuye K, et al. Prognostic factors in patients with locally advanced pancreatic carcinoma receiving chemoradiotherapy. *Cancer*. 2001;91:490–495.
22. Yang GY, Wagner TD, Fuss M, et al. Multimodality approaches for pancreatic cancer. *CA Cancer J Clin*. 2005;55:352–367.
23. Calvet X, Bruit J, Ginès P, et al. Prognostic factors of hepatocellular carcinoma in the west: a multivariate analysis of 206 patients. *Hepatology*. 1990;12:753–760.
24. Furuse J, Maru Y, Yoshino M, et al. Hepatic arterial infusion of 5-fluorouracil for liver metastases from pancreatic carcinoma: results from a pilot study. *Hepatogastroenterology*. 2001;48:208–211.
25. Ishii H, Furuse J, Nagase M, et al. Hepatic arterial infusion of 5-fluorouracil and extrabeam radiotherapy for liver metastases from pancreatic carcinoma. *Hepatogastroenterology*. 2004;51:1175–1178.
26. Dragovich T, Burris H, Loehrer P, et al. Gemcitabine plus celecoxib in patients with advanced or metastatic pancreatic adenocarcinoma: results of a phase II trial. *Am J Oncol*. 2008;31:157–162.
27. Morizane C, Okusaka T, Furuse J, et al. A phase II study of S-1 in gemcitabine-refractory metastatic pancreatic cancer. *Cancer Chemother Pharmacol*. 2009;63:313–319.
28. Fujino Y, Ueda T, Kamigaki T, et al. Impact of gemcitabine on the survival of patients with stage IV pancreatic cancer. *Pancreas*. 2007;34:335–339.
29. Krishnan S, Rana V, Janjan NA, et al. Prognostic factors in patients with unresectable locally advanced pancreatic adenocarcinoma treated with chemoradiation. *Cancer*. 2006;107:2589–2596.
30. Park JK, Yoon YB, Kim YT, et al. Survival and prognostic factors of unresectable pancreatic cancer. *J Clin Gastroenterol*. 2008;42:86–91.
31. Tanaka T, Ikeda M, Okusaka T, et al. Prognostic factors in Japanese patients with advanced pancreatic cancer treated with single-agent gemcitabine as first-line therapy. *Jpn J Clin Oncol*. 2008;38(11): 755–761.
32. Maréchal R, Demols A, Gay F, et al. Prognostic factors and prognostic index for chemonaïve and gemcitabine-refractory patients with advanced pancreatic cancer. *Oncology*. 2007;73(1–2):41–51.
33. Buchler MW, Kleeff J, Friess H. Surgical treatment of pancreatic cancer. *J Am Coll Surg*. 2007;205:S81–S86.
34. Shrikhande SV, Kleeff J, Reiser C, et al. Pancreatic resection for M1 pancreatic ductal adenocarcinoma. *Ann Surg Oncol*. 2007;14:118–127.
35. Hazard L, Tward JD, Szabo A, et al. Radiation therapy is associated with improved survival in patients with pancreatic adenocarcinoma: results of a study from the Surveillance, Epidemiology, and End Results (SEER) registry data. *Cancer*. 2007;110:2191–2201.
36. Wu F, Wang ZB, Zhu H, et al. Feasibility of US-guided high-intensity focused ultrasound treatment in patients with advanced pancreatic cancer: initial experience. *Radiology*. 2005;236:1034–1040.
37. Fu J, Liu LM, Shen J, et al. Effects of QYHJ decoction on expression of MDR in transplantation tumors of pancreatic cancer in nude mice. *Chin J Basic Med Tradit Chin Med*. 2007;13:289–291.