Pancreatology 17 (2017) 773–781

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Factors influencing survival of patients with pancreatic adenocarcinoma and synchronous liver metastases receiving palliative care

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ARTICLE INFO

Article history:
Received 23 April 2017
Accepted 7 July 2017
Available online 8 July 2017

Keywords:
Pancreatic adenocarcinoma
Liver metastases
Palliative care
Prognosis
Survival analysis

ABSTRACT

Background and aims: Patients with pancreatic ductal adenocarcinoma and synchronous liver metastases (PACLM) have an extremely limited life expectancy. We performed a single-center analysis to explore the clinical results and prognostic factors of patients with PACLM receiving palliative care.
Methods: We retrospectively reviewed 189 patients undergoing palliative care at Tianjin Medical University Cancer Hospital over a 15-year period. Clinical characteristics, survival condition, and factors associated with survival were analyzed. Treatment methods included palliative bypass surgery, percutaneous transhepatic cholangiodrainage, drug analgesia, symptomatic treatment, and other nutritional or supportive measures.
Results: The overall survival (OS) was 3.6 months for all patients. Multivariate analysis for clinical features showed that Karnofsky performance score (KPS), ascites, cigarette smoking, primary tumor size, and lactate dehydrogenase (LDH) were prognostic variables with statistical significance ($P < 0.05$). The patients were classified into three groups of patients according to how many of these 5 risk factors were present: 0–1, 2, or 3–5 risk factors. The median OS of the 3 groups of patients were 5.0, 3.3, and 2.5 months, respectively, with a notable statistical significance ($P < 0.0001$).
Conclusions: KPS<80, ascites, cigarette smoking, primary tumor size≥5 cm, and LDH≥250U/L are effective predictive factors of poor prognosis for patients with PACLM. The stratification of treatment outcome groups based on these factors facilitates evaluation of individual prognosis and can guide clinical decisions.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most fatal malignancies with increased morbidity and mortality, and there has no major treatment breakthrough [1]. In the United States, the 5-year survival rate of PDAC is only about 6% [2]. The main reason for this low survival rate is because a large majority of the patients present with unresectable metastases. Liver is the most common organ for distant metastases of PDAC, and even after curative surgery for resectable disease, more than 62% of patients will develop multiple liver metastases [3,4]. Patients with pancreatic ductal adenocarcinoma and synchronous liver metastases, PACLM, face an even worse outcome [5,6]. Although palliative chemotherapy regimens such as FOLFIRINOX, or gemcitabine plus nab-paclitaxel have shown survival benefits for patients with metastatic PDAC [7,8], some patients with PACLM have not been able to try aggressive anti-tumor approaches due to poor performance status or concomitant organ dysfunction. Therefore, palliative care has played an important role for these patients.

Previous reports about advanced PDAC have always focused on

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http://dx.doi.org/10.1016/j.pan.2017.07.002
1424-3903/

the value of aggressive anti-tumor therapies, yet little attention is paid to palliative care. In addition, there is little clinical data about the prognostic analysis of patients with PACLM receiving palliative care. To address this need, the aim of this study was to explore the survival results and prognostic factors of patients undergoing palliative care.

Patients and methods

Patients

From 2001 to 2015, a total of 1298 patients were diagnosed with PDAC at the Tianjin Medical University Cancer Hospital (TMUCH). Of these patients, 507 were histologically confirmed as having PACLM (defined as the detection of liver metastases at or before diagnosis of the primary PDAC) and 189 of them who received palliative treatment alone were retrospectively analyzed. The flow chart shown in Fig. 1 depicts the process of case selection.

Palliative therapeutic methods

The 189 patients included in this study were administered palliative care based on biliary drainage and analgesia. There are four main reasons that these patients received palliative care only: 163 (86.2%) patients refused more aggressive treatment (including chemotherapy, radiation therapy, interventional therapy, and physiotherapy) immediately after PACLM diagnosis, 14 (7.4%) presented extremely poor performance status (KPS $\leq$ 60), and 12 (6.3%) had organ dysfunction or other chronic diseases (chronic renal insufficiency, chronic cardiac insufficiency, or chronic obstructive pulmonary disease). Palliative therapeutic methods include bypass surgery, percutaneous transhepatic cholangial drainage (PTCD), drug analgesia, percutaneous neurolytic coelial plexus block, and best supportive care. Patients may receive one or more of these palliative treatment modalities. The institutional ethics committee of TMUCH approved this study. All methods were performed according to Chinese bioethical regulations. Patients who refused to accept aggressive treatments signed written informed consents.

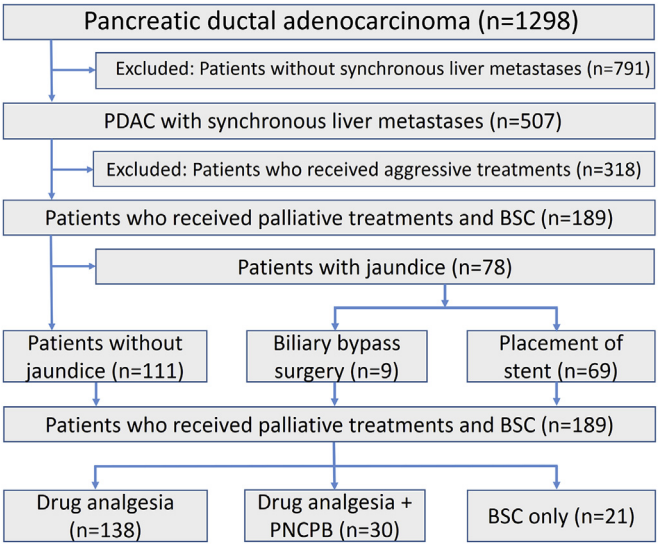

Fig. 1. The flow chart of case selection. PDAC pancreatic ductal adenocarcinoma, PNCPB percutaneous celiac plexus block, BSC best supportive care.

Statistical analysis

Follow-up was scheduled every 3 months after discontinuation of treatment. OS was measured from the date of diagnosis until death from any cause or censored at last follow-up. Curves were plotted using Kaplan-Meier methodology, and differences between arms were evaluated by the log-rank test. Clinical variables with $P \leq 0.05$ in univariate analysis were entered into a multivariate stepwise regression analysis by application of the cox proportional hazard model. Data were analyzed by STATA 12.0 (College Station, Tex, US), tests were two-sided, and a $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 189 patients were retrospectively collected from January 2001 to December 2015 at TMUCH. The studied patients' characteristics are shown in Table 1. Palliative treatments designed to relieve obstructive jaundice and pain are described in Fig. 1.

Survival

The median OS was 3.6 months, and OS rates at 3 and 6 months were 62.4% and 19.9%, respectively (Fig. 2.). After a median follow-up period of 35.2 months (range 5.1–193.1 months), 174 patients (92.1%) had died within 18 months, and 15 patients (7.9%) were unable to be contacted. The longest survival time was 526 days and the shortest was just 13 days for the whole group.

Factors associated with survival

Table 1 shows the results of univariate analyses of factors influencing patient prognosis. The univariate analysis revealed that KPS<80, heavy alcohol intake, active smoker, primary tumors localized in the whole pancreas, primary tumor size≥5 cm, extent of liver involvement≥25%, regional lymph node metastases, extrahepatic metastases, ascites, serum albumin<35 (g/L), CA19-9≥1000 (U/ml), glutamyl transferase (GGT)≥54 (U/L), c-reactive protein (CRP)≥50 (mg/L) and LDH≥250 (U/L) were associated with significantly poorer survival ($P < 0.05$). We then applied a multivariate model and included all variables with a P-value≤0.05 in univariate analyses. This analysis allowed us to identify 5 risk factors as independent markers of shortened survival: KPS <80, active smoker, ascites, primary tumor size≥5 cm, and LDH≥250 (U/L) (Fig. 3, Table 2).

Subgroup analyses revealed that patients of active smokers had a worse prognosis in the elderly group (≥60 years, $P = 0.02$), but the difference was not evident in patients aged<60 years ($P = 0.37$) (Fig. 4A–C). In addition, larger pancreatic tumor size (≥5 cm) may appear to be a more valuable adverse prognostic factor in the evaluation of patients who survived 4 months or greater ($P = 0.001$) (Fig. 5A–C). However, for patients with less than 4 months of survival, the impact of liver involvement on survival was significantly greater than the primary tumor size ($P = 0.01$) (Fig. 5 D).

All patients were further stratified according to the number of applicable risk factors. The results demonstrated that patients with none or one of these risk factors had a longer median OS than patients with 2 risk factors or those with more than 3 risk factors (median OS: 5.0 vs. 3.3 vs. 2.5 months, $P < 0.001$) (Fig. 6).

Patients who survived more than 6 months

Of the 189 patients, 30 (15.9%) were alive at least 6 months after