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Original Research

A case-matched comparison study of total pancreatectomy versus pancreaticoduodenectomy for patients with pancreatic ductal adenocarcinoma

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ABSTRACT

Background: Total pancreatectomy (TP) is considered a viable option in some selected patients with pancreatic ductaladenocarcinoma (PDAC). The aim of this study was to compare the clinical outcomes between TP and pancreaticoduodenectomy (PD) in patients with PDAC.

Materials and methods: A total of 375 patients were selected from our center's database in China and classified into two groups: the PD group (n = 325) and the TP group (n = 50). A matched-pair analysis of the patients was conducted with a ratio of 1:1. Univariate and multivariate survival analyses were performed for overall survival.

Results: Overall morbidity was lower in the PD group than in the TP group (31.4% vs 52%, respectively, $P = 0.004$). However, no significant difference was observed in major morbidity between the two groups (24.9% vs 30%, $P = 0.455$). The rates of 5-year overall ($P = 0.043$) and disease-free ($P = 0.037$) survival were significantly higher in the PD group. Furthermore, the univariate and multivariate analyses revealed that adjuvant chemotherapy (HR = 0.684, 95%CI = 0.545–0.860, $P = 0.001$) and margin resection status (HR = 1.666, 95%CI = 1.196–2.321, $P = 0.003$) were significant prognostic factors. After the matched-pair analysis, there were no significant differences between the two groups regarding postoperative complications and overall survival. However, the matched PD group had greater estimated blood loss ($P = 0.037$) and blood transfusion (56% vs 36%, $P = 0.045$).

Conclusion: From our study, the postoperative outcomes and survival time of TP are similar to those of matched PD. It seems reasonable to suggest that TP can be considered as safe, feasible, and efficacious as PD for patients with PDAC.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) was the fourth leading cause of cancer-related death in the United States in 2016 among both males and females [1]. Furthermore, the incidence of new cases and mortality are nearly equal in China [2]. Surgical resection remains the only method to obtain a cure. However, only 8% of patients are diagnosed in the early stages, and of those, only 20% are candidates for surgical resection [3,4]. To our knowledge, there are three main surgical procedures for PDAC according to the location of the tumor, namely, pancreaticoduodenectomy (PD), total pancreatectomy (TP) and distal pancreatectomy (DP). However, the 5-year overall survival rate is approximately 20% after radical PD in high-volume centers [5–7].

According to the literature, the first modern report of TP for PDAC was by Rockey in 1943; however, the patient died in the perioperative period due to bile leakage [8]. Earlier surgical indications were based on the premise of multifocality of the adenocarcinoma of the pancreas and it was presumed that TP would achieve a microscopically negative surgical resection margin (R0) compared to the other two surgical procedures [9,10]. Moreover, some pancreatic surgeons have suggested elective TP over PD in high-risk cases to avoid a potential postoperative pancreatic fistula (POPF) and subsequent mortality and morbidity after PD [11,12]. However, several previous studies have suggested that TP

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was associated with higher operative morbidity and mortality compared to PD [13–15]. Furthermore, the permanent pancreatic endocrine and exocrine insufficiency induced by TP has led to concerns about its potentially detrimental impact on long-term survival and quality of life (QOL) [16]. Some investigators have even argued that PDAC requiring TP was inherently associated with poor long-term survival [17].

Recently, due to improvements in surgical techniques and perioperative care, including better pancreatic enzyme formulas and long-acting insulin [18–20], several reports have argued that TP can be performed safely with minimal impact on endocrine and exocrine dysfunction and QOL. However, performing TP for PDAC compared to PD is more controversial. Some studies reported that TP led to similar or worse survival times than PD for patients with PDAC [13,21,22]. However, one study [23] suggested that TP resulted in better long-term survival than PD in patients with PDAC. Because of these conflicting results, TP has not been recommended as a routine treatment for patients with PDAC [24].

Currently, no prospective randomized study comparing these two methods has been reported. In addition, most comparative studies suffered from several methodological problems, such as a lack of adjustment for tumor-specific factors or the inclusion of all pancreatic tumors with different pathological types. Therefore, the aim of this study was to present our institutional experience in evaluating whether TP can be considered as feasible, safe, and efficacious as PD in patients with PDAC by comparing the two procedures relative to postoperative outcome and long-term survival. Additionally, a matched-pair analysis was used to balance the selection bias.

2. Patients and methods

2.1. Study design and ethical standard

This study was a single-center, retrospective observational study with prospectively collected data. All patients who underwent TP and PD for PDAC at our institute from March 2009 to October 2015 were compared. This study was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. This study was approved by the relevant Ethics Committee and informed consent was obtained from all patients.

2.2. Study population

Only patients with histologically proven PDAC were included in the current study. Patients with pancreatic neuroendocrine tumor, pancreatic solid pseudopapillary neoplasm, intraductal papillary mucinous neoplasms (IPMN), IPMN-associated adenocarcinoma, primary cystadenocarcinomas and other cystic lesions were excluded. In addition, all operations were completed in one stage and were non-emergencies. Patients who underwent neoadjuvant chemotherapy or received other chemotherapy drugs or radiotherapy were excluded.

2.3. Surgical techniques and indication

TP was divided into 3 steps: (1) mobilization of the whole pancreas through the mobilization of the right colon and hepatic flexure, a wide Kocher maneuver, and gastrocolicli gament division; (2) mobilization of the spleen for splenectomy; and (3) ligation of the splenic vessels and gastroduodenal artery. In PD cases, the digestive tract was always reconstructed with a pancreaticojejunostomy using the Child method. TP was preferred under the following conditions in our hospital: (1) the presence of multi-focal neoplastic lesions; (2) the suspected tumor involved the pancreatic neck and either extended to or extended from the pancreatic head; (3) positive resection margins in the pancreatic stump demonstrated by repeated frozen sections; and (4) evidence of difficult vascular reconstruction.

2.4. Postoperative treatment and follow-up

Postoperatively, in all patients who underwent PD, somatostatin analogs were administered postoperatively for 7 days, except in the presence of pancreatic fistula (PF), in which case they were continued. All patients with a postoperative diagnosis of diabetes and exocrine insufficiency were given pancreatic enzyme supplementation and were referred to the endocrinology team, which provided diabetes-related education, discharge instructions, and follow-up care. Finally, all patients were followed up by the surgeons and the nurse team. Gemcitabine (an intravenous infusion of 1000 mg/m^2) was given on days 1, 8, and 15 of each cycle, which was repeated every 4 weeks. All patients were followed up by our team every 3–6 months. In this study, the patients were followed up until the end of July 2016 via telephone conversations or outpatient clinic appointments. The median follow-up time was 23 months (3–91 months).

2.5. Data collection and study definitions

Data were obtained from our database and included demographics, American Society of Anesthesiology (ASA) scores and the presence of major comorbidities (chronic obstructive pulmonary disease, hypertension, or diabetes mellitus). Operative details including the type of pancreatic resection, associated vascular resection, estimated blood loss, blood transfusion, and operation time were obtained from nurse, anesthesiologist, and surgeon reports. Pathological data of the resected surgical specimen, including tumor size, differentiation, lymph node metastases, vascular invasion, perineural invasion, resection margin and tumor differentiation were analyzed. For tumors, pathological data included T and N status according to the 8th American Joint Committee on Cancer/Union for International Cancer Control TNM classification [25]. R1 resection was defined as a microscopic residual tumor due to the presence of tumor cells at the surface of the resection margin (the 0-mm rule) according to the classification of the International Union Against Cancer (UICC) [26]. Postoperative complications were extracted from daily progress notes and discharge summaries.

Mortality was defined as the number of deaths occurring during hospitalization or within 30 days after surgery. Overall morbidity was defined as any complication following surgery up to the day of discharge, which was classified according to the Clavien-Dindo classification [27], and major morbidity was defined as a complication of grade III or greater. Hypoglycemia was defined as a random blood sugar level of less than 2.8 mmol/L causing symptoms. Readmission rate was defined as readmission within 30 days of hospital discharge. Operating time was defined as the time from incision to suturing of the skin. Postoperative hospital stay was calculated as the interval from the day of surgery to the date of discharge.

2.6. Study outcomes

The primary study outcome was overall survival (OS) and the secondary study outcomes included disease-free survival (DFS), morbidity and mortality in the two groups.

2.7. Matched-pair analysis

To evaluate whether the perioperative outcomes and postoperative survival time were different for TP and PD, a matched-pair analysis of patients who underwent either TP or PD was performed. Patients were matched for age, gender, tumor size, adjuvant chemotherapy and resection margin status.

2.8. Literature search

PubMed (Medline), EMBASE, the Science Citation Index Expanded and the Cochrane Central Register of Controlled Trials in the Cochrane