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Survival, morbidity and mortality of pancreatic adenocarcinoma after pancreaticoduodenectomy with a total mesopancreas excision

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ABSTRACT

Introduction: pancreatic adenocarcinoma is the most common malignancy in the periampullary region, with a five-year survival rate around 20%.

Objective: the goal of our study was to determine the survival and safety data of a number of patients that underwent a cephalic duodenopancreatectomy (CDP) with total mesopancreas excision (TMPE).

Material and methods: a prospective observational study was performed of 114 patients with pancreatic adenocarcinoma who underwent duodenopancreatectomy and TMPE over the period 2008-2017. Demographic variables, tumor stage, number of lymph nodes excised, lymph node ratio, R classification, the prognostic factor disease-free interval and survival were all assessed in a multivariate analysis.

Results: complications were reported for 54 (47.3%) patients, of which 22 (19.3%) were categorized as serious. The mortality rate was 4.3% and the mean follow-up was 26.2 months. During this period, 73 (64%) patients relapsed after a mean interval of 40.9 months. The relapse pattern was mainly hepatic (26.3%), followed by local relapse

(20%). Mean survival was 40.38 and actuarial survival was 26.6% at five years. Relapse-related factors included stage T3 or higher (RR 8.1 [1.1-61]) and an R1 resection (RR 13.4 [2.7-66.5]) and survival-related factors included an R1 resection (RR 10.7 [2.5-46.2]).

Conclusion: TMPE ensures an adequate lymphadenectomy and lymph node ratio according to reported standards. The survival of patients that have undergone surgery for pancreatic adenocarcinoma in our institution is 68.4% at one year and 26.6% at five years. An R1 resection is the primary factor for both relapse and survival.

INTRODUCTION

Pancreatic head adenocarcinoma (ADC) is the most common malignancy in the periampullary region. Approximately 20% of diagnosed patients undergo a resection and the overall survival (OS) at five years is around 20-25% (1,2). In the past few decades, modifications to the classical pancreaticoduodenectomy (PD) technique were proposed that primarily aimed to provide surgical margins free from microscopic residual tumor (R0). This is associated with a decrease in the local recurrence rate and an increased survival (3). The total mesopancreas excision (TMPE) concept arose in this setting, which enhanced the oncological radical nature for PD. Gockel (4) defined the mesopancreas as the structure that contains the connective tissue extending between the superior mesenteric artery (SMA) and the pancreatic head and uncinate process. This included the inferior pancreaticoduodenal artery and lymphatic, neural and vascular tissue to the Treitz fascia. Therefore, TMPE involves the complete excision of the lymphatic, neural and vascular tissue in the mesopancreas in an attempt to optimize local disease control, provide an R0 resection and improve postoperative staging.

Various approaches to mesenteric vessels have been described. The posterior SMA first approach, as described by Pessaux, allows a TMPE (5,6). Several theoretical advantages are associated with this technique. These include early assessment of SMA infiltration before irreversible maneuvers are performed, detection and preservation of arterial anatomic variants, reduced venous congestion in the specimen, improved retroperitoneal and lymphadenectomy margins (TMPE) and exposure of the

splenomesenteric-portal axis if vascular resection is required (7,8).

Recent reports of TMPE results indicate a high percentage of R0 resections (9), although long-term survival and the pattern of recurrence are not usually mentioned (10). Thus, this study aimed to determine the recurrence and survival rates of the patients with ADC in the pancreas head after PD with TMPE in one institution. Furthermore, the technical safety, patterns of recurrence, survival and prognostic factors (PFs) were also assessed.

MATERIAL AND METHODS

Study design

An observational study was performed of a prospective database of 114 consecutive patients diagnosed with pancreatic head ADC, who underwent PD and TMPE from April 2008 to December 2017. During this period, 274 PDs were performed in our center. Patients with unresectable lesions were excluded from the study. An SMA first approach with TMPE was used for all 224 tumor cases. This included 114 pancreas head ADCs, 37 papillary ADCs, 37 cholangiocarcinomas, 22 intraductal mucinous papillary neoplasms and 14 neuroendocrine tumors. A multidisciplinary committee was involved in the surgical approach. Neoadjuvant chemotherapy was indicated for patients with borderline lesions (11) with three cycles of folfirinox or gemcitabine plus Abraxane® treatment. Treatment response was assessed before surgery. Following the PD, the patients were referred to the same multidisciplinary committee for adjuvant therapy according to pathology findings, age and patient status. Primary adjuvant schemes included folfirinox or gemcitabine plus Abraxane® for large tumors ($T \geq 3$) or tumors with lymph node involvement and radiation therapy for patients with an R1 resection. All patients signed an informed consent for the surgical procedure in accordance with the hospital protocol, as approved by the Ethics Committee.

Surgical technique

The surgery was performed by two of the three surgeons within the unit, using a standardized resection and reconstruction technique. This consisted of PD with an SMA first approach, according to Pessaux (6) and lymphadenectomy (12) with TMPE

(4). This included the space between the celiac trunk, SMA and superior mesenteric vein, whilst avoiding a circumferential SMA dissection. Pancreatic reconstruction was performed with a pancreaticogastrostomy (type I-B S0) (13) as the technique of choice, according to Delcore (14).

Postoperative care

Postoperative care was standardized using a clinical plan (15).

Variables

A prospective database was designed using the FileMaker® program with over 100 variables. The variables included were: demography, ASA classification (16), body mass index (BMI), diagnosis, surgical procedures, procedure date, TNM and R classification, neoadjuvant or adjuvant therapy, surgeons, surgical complications according to the Clavien-Dindo classification (17) (grades I, II, III-A, III-B, IVa, IVb, V) and ISGPS classification for postoperative pancreatic fistula (18), delayed gastric emptying (19) and post-pancreatectomy bleeding (20). Furthermore, data regarding re-intervention, infection, admission to intensive care, the need for radiographic, endoscopic or transfusion procedures, mortality and readmission were also collected. Overall survival (OS) and recurrence-free survival (RFS) were assessed. The analysis of survival predictors included demographic variables, TNM stage (21), total number of lymph nodes (TLN) removed, lymph node ratio (22) (LNR: number of metastatic lymph nodes/TLN) and R classification (23) (R0: no residual tumor; R1: tumor within 1 mm of the resection margin and R2: residual tumor).

Statistical analysis

Survival was assessed using the Kaplan-Meier approach. A Cox regression model was constructed using the main associated prognostic factors. Data were analyzed using the SPSS 22.0s statistical package. Statistical significance was set at a p-value ≤ 0.05.

RESULTS

Demography and surgery

The median age of the patients was 69 years (38-84) and males were slightly more frequent in the cohort (55%) (Table 1). Patients were primarily ASA II (50%) and ASA III (42%). A total of 10.5% of patients received neoadjuvant therapy as they were considered as borderline resectable and 63% received adjuvant chemotherapy postoperatively, according to pathology findings and assessment by the Oncology Department. Eighty-six percent of tumors were finally staged as T3 and 75 (65.8%) patients had affected lymph nodes. The median number of resected lymph nodes was 23 (7-58), median LNR was 0.07 (0-0.62) and R0 resections amounted to 67.5%. The median surgery duration was 340 minutes (210-540).

Morbidity and mortality

Table 2 shows the morbidity and mortality data of the cohort. A total of 54 (47.3%) patients had some type of postoperative complication, including readmission within 30 days. Of these, 22 (19.3%) were classified as severe (≥ 3) according to the Clavien-Dindo classification. The proportion of re-interventions was 9.6% and of readmissions was 13%. Postoperative mortality at 90 days was 4.3% and the median hospital stay was 9.5 days (6-46).

Overall survival and recurrence-free survival

The median follow-up was 48.3 months, as estimated using the reverse Kaplan-Meier method. Median OS was 24.7 months (95% CI, 12.8-36.7), with an estimated OS of 68.4% at one year, 39.3% at three years and 26.6% at five years (Fig. 1). During this period, 71 (62.3%) patients had a tumor recurrence, with a median RFS of 16.1 months (95% CI, 6.5-25.8) (Fig. 2). The pattern of recurrence is shown in table 3; the locations were pooled together. Thirty-five of 71 patients had hepatic recurrence (50.7%); 27, local recurrence (39.1%); 18 (26%), peritoneal recurrence; and 18 (26%), distant recurrence.

Prognostic factors for OS and RFS

The primary prognostic factors (PFs) for survival and recurrence were assessed (Table 4). According to the multivariate analysis, the PFs associated with RFS included stage

T3 or higher (RR 8.1 [1.1-61]) and an R1 resection (RR 13.4 [2.7-66.5]). An R1 resection was the only PF for recurrence (RR 10.7 [2.5-46.2]). Finally, survival analysis was performed according to R classification. The median OS for patients with an R0 resection was 48.5 months (95% CI, 29.7-67.3) and 11.16 months (95% CI, 6.8-15.5) for patients with an R1 resection.

DISCUSSION

The first part of our study focused on the assessment of the safety of patients undergoing PD with TMPE, using a morbidity and mortality analysis according to the Clavien-Dindo classification. Recently, Sabater analyzed 15 series available in Spain (24) and proposed a set of pancreatic cancer surgery quality standards, which included various techniques. The morbidity rate in our series using TMPE was 47.3%, which is lower than the mean of 58% reported by the Sabater study groups and is also lower than the maximum standard suggested of 73%. The mortality rate in our series was similar to the average value obtained, around 4%. The re-intervention rate was 9.6% and the mean hospital stay was 12 days, which are lower than the reported standards of 11% and 18 days, respectively. Therefore, TMPE appears to be a safe technique, with no increase in morbidity and mortality *versus* the classical PD approach.

Long-term OS for patients with pancreatic ADC remains between 20-25%, despite a standardized PD technique and improved chemotherapy (25). In order to optimize oncological results for pancreatic cancer, PD should meet the following oncologic standards: R0 surgery, over 12-15 excised lymph nodes (26,27) and an LNR lower than 0.2 (28,29). Furthermore, a multidisciplinary management is required (neo-/adjuvant) (30).

Theoretically, TMPE achieves a complete removal of the lymphatic, vascular and neural tissues in the mesopancreas in an attempt to enhance local disease control by increasing the R0 surgery rates. In our study, R1 surgery was the only independent predictor of survival (RR 10.7 [2.5-46.2]). Extended lymphadenectomy has failed to increase OS and does result in higher morbidity (31,32). With regard to recurrence, the median RFS in our series was 16.1 months and 62.3% of patients had a recurrence during follow-up. The most common locations were hepatic (50.7%) and local (39.1%)

recurrences. Hishinuma (33) analyzed in 2006 the results of 27 autopsies of patients who died from recurrent pancreatic ADC, who were managed with PD and extended lymphadenectomy. This study concluded that 75% had a local recurrence, 50% had hepatic recurrence and 33%, peritoneal involvement. The percentages are in excess of 100% as some patients had multiple recurrence sites. The most common combination was local and hepatic recurrence in this study, *versus* isolated hepatic recurrence in our study. Sugiura (34) reported a retrospective study in 2013 of 208 patients that underwent surgery for pancreatic ADC with curative intent and standard lymphadenectomy. This study found a recurrence rate of 77%, 46% for local recurrence (local and nodal), 45% for hepatic, 19% for peritoneal and 22% for other locations. Our results are similar to those reported, but with a slightly lower rate of local recurrence (Table 3).

Although the mesopancreas was described more than ten years ago and multiple studies have discussed the TMPE technique, the literature remains sparse on the survival outcome of these patients (10). The first report of TMPE outcome was published by Adham (9) in 2012. This study included 26 patients with an R0 rate of 80% and a mean number of 24 excised lymph nodes. Kawabata (35,36) reported a study of 34 patients, with an R0 rate of 73% and a mean of 34 excised lymph nodes. The study by Wu et al. in 2016 (37) of 120 patients reported 71.6% of R0 resections. Only the study by Kawabata reports survival outcomes, with a median survival of 18.3 months and 35.2% at three years. Our results of 114 patients are similar in terms of the median number of lymph nodes removed (23 nodes), with a proportion of R0 resections of 67.5% and a median OS of 24.7 months and 39.3% at three years.

Finally, we analyzed PFs for recurrence and OS. As in most reports, the proportion of R1 resections and tumors staged as T3 or higher represent PFs associated with RFS, whereas only R1 resections were associated with a poorer OS. There was no association in our series with other prognosis-related PFs, such as lymph node involvement, number of excised lymph nodes and lymph node ratio. A study of the US National Cancer Database (38) assessed the role of excised lymph node number in patients with pancreatic adenocarcinoma after PD. The mean number of excised nodes was eleven and poorer OS outcomes were reported for patients with 0-6 affected

lymph nodes, particularly when compared to patients with over 15 nodes removed. It is possible that this factor did not reach significance in our study due to the fact that the mean number of excised lymph nodes with TMPE was 24 and only three patients had fewer than 15 nodes in their lymphadenectomy specimen.

The OS results achieved at five years with TMPE in our study are at the upper end of the range reported by the main series (39). The local recurrence findings were lower than those reported by other groups, with either classical or extended lymphadenectomy. This study has a number of limitations due to its observational nature and to the fact that only one approach was used and there was no comparison with the classic procedure. Furthermore, the study was performed for eight years in order to reach an adequate number of cases. During this time, the international unresectability criteria and chemotherapy schemes underwent several modifications. However, the patients in the final part of the study had a shorter follow-up, which may have an impact on the actual recurrence or survival outcomes at 60 months.

However, these results are consistent with other international publications (29,40-42). We found that TMPE is associated with a lower percentage of R1 resections, an increased number of excised lymph nodes in the specimen and a lower mean LNR. These factors have led to improved five-year survival rates in other studies (30). Therefore, it may reasonably be claimed that TMPE optimizes local disease control. However, these results based on observational studies should be confirmed by randomized clinical trial to assess the OS and pattern of recurrence of patients undergoing classical PD *versus* TMPE.

CONCLUSIONS

TMPE ensures an adequate lymphadenectomy and lymph node ratio according to published standards.

The OS of patients with PD for pancreatic head ADC in our center is 68.4% at one year, 39.3% at three years and 26.6% at five years.

The primary PF for pancreatic ADC recurrence and mortality is an R1 resection.

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Table 1. Demographic and surgical data

	CDP with TMPE for ADC (n = 114)
Median age (range)	69 years (38-84)
Male gender, n (%)	63 (55.3%)
Median BMI (range)	26 (19-58)
ASA classification, n (%)	
ASA I	7 (6.1%)
ASA II	57 (50%)
ASA III	48 (42.1%)
ASA IV	2 (1.8%)
T classification, n (%)	
T1	7 (6.1%)
T2	4 (3.5%)
T3	98 (86%)
T4	5 (4.4%)
N classification	
N0	39 (34.2%)
N1	74 (64.9%)
N2	1 (0.9%)
Median of excised lymph nodes (range)	23 (7-58)
Fewer than 15 excised nodes, n (%)	3 (2.6%)
Median lymph node ratio (range)	0.07 (0-0.62)
Lymph node ratio > 0.2, n (%)	21 (18.4%)
R classification, n (%)	
R0	77 (67.5%)
R1	37(32.4%)
R2	0
Adjuvant chemotherapy, n (%)	72 (63.2%)
Neoadjuvant chemotherapy, n (%)	12 (10.5%)
Median surgical time (range)	340 minutes (210-540)

CDP: cephalic duodenopancreatectomy; TMPE: total mesopancreas excision; ADC: adenocarcinoma; ASA: American Society of Anesthesiologists; BMI: body mass index.

Table 2. Morbidity and mortality for the TMPE series

Complications, n (%)	54 (47.3%)
Clavien-Dindo ≥ 3, n (%)	22 (19.3%)
Reinterventions, n (%)	11 (9.6%)
Mortality at 90 days, n (%)	5 (4.3%)
Median stay (range)	9.5 days (6-46)
Readmissions at 30 days, n (%)	15 (13%)

Table 3. Recurrence pattern

Location	*n (%)*
Hepatic	16 (14%)
Hepatic and local	9 (7.9%)
Hepatic and peritoneal	5 (4.4%)
Hepatic and other distant	1 (0.8%)
Hepatic, local and other distant	2 (1.7%)
Hepatic, local and peritoneal	2 (1.7%)
Local	8 (7%)
Local and other distant	4 (3.5%)
Local and peritoneal	2 (1.7%)
Peritoneal	9 (7.8%)
Other distant (non-hepatic)	11 (9.6%)
Not recorded	2 (1.7%)

Table 4. Multivariate analysis of predictors for recurrence-free survival (RFS) and overall survival (OS)

	RFS		*OS*	
	RR (95% CI)	*p-value*	*RR (95% CI)*	*p-value*
Age > 70 years	1.6 (0.6-4.4)	0.32	2.1 (0.8-5.8)	0.12
Complication	1.5 (0.6-4)	0.35	1.2 (0.5-3.1)	0.67
T ≥ 3	*8.1 (1.1-61)*	*0.04*	4.45 (0.8-24.4)	0.08
N+	2 (0.7-6)	0.19	1.55 (0.5-4.8)	0.44
Lymph node ratio > 0.2	1.8 (0.4-7)	0.41	0.97 (0.27-3.5)	0.9
R1 resection	*13.4 (2.7-66.5)*	*0.001*	*10.7 (2.5-46.2)*	*0.001*
Adjuvant therapy	1.5 (0.5-4.3)	0.45	1.28 (0.4-3.8)	0.6
Neoadjuvant therapy	1.1 (0.24-4.7)	0.9	0.62 (0.15-2.5)	0.5

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Fig. 1. Overall survival curve for patients undergoing TMPE for pancreatic adenocarcinoma (n 114). Median follow-up: 48.3 months. Median OS: 24.7 months (95% CI: 12.8-36.7). OS at one, three and five years was 68.4%, 39.3% and 26.6%, respectively.

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Fig. 2. Recurrence-free survival (RFS) curve for patients undergoing TMPE for pancreatic adenocarcinoma (n 114). Median follow-up: 48.3 months. Median RFS: 16.1 months (95% CI: 6.5-25.8). RFS at one, three and five years was 54.5%, 36.7% and 28%, respectively.

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Fig. 3. Overall survival curves for patients according to their R classification. Median OS for R0 patients: 48.528 months (95% CI: 29.7-67.3). Median OS for R1 patients: 11.165 months (95% CI: 6.8-15.5).