Journal of BUON **17:** 299-303, 2012

ORIGINAL ARTICLE

Pancreatoduodenectomy for pancreatic cancer in a low volume institution

P. Lampropoulos[1], A. Vezakis[2], N. Paschalidis[1], E. Balitsaris[1], A. Zizi-Sermpetzoglou[3], A. Hadjimarcou[1], S. Rizos[1]

[1]Tzaneio General Hospital, First Surgical Department; Piraeus; [2]Aretaieio Hospital, Department of Surgery, University, of Athens, Athens; [3]Tzaneio General Hospital, Department of Pathology, Piraeus, Greece

Summary

Purpose: *To report the patient morbidity and mortality rates following pancreatoduodenectomy (PD) carried out in our low volume institution, and compare our results with results from other high volume institutions.*

Methods: *A retrospective analysis was conducted on patients with pancreatic malignancies surgically treated with PD from 2005 to 2010 in our institution. Data were collected with particular emphasis on morbidity and mortality rates. All patients were followed from the date of discharge to the date of death or status at the last follow-up (July 2011).*

Results: *In a period of 5 years 42 patients underwent PD. Morbidity rates were as follows: 11.9% wound infections, 21.4% pancreatic fistulae, 23.8% delayed gastric emptying (DGE), 14.3% hemorrhage, and 7.1% biliary leak. Two patients required re-laparotomy one for delayed hemorrhage and one for sepsis. The mortality rate was 7.1%. The 2-year survival rate was 45.1% and the median survival 22 months.*

Conclusion: *PD in our low volume institution had high morbidity and mortality rates compared with results published in the literature. There is a need, however, to establish a policy for referral of patients with pancreatic cancer to other centers with a higher number of resections, in order to decrease morbidity and mortality rates.*

Key words: low volume institution, morbidity, mortality, pancreatic cancer, pancreatoduodenectomy

Introduction

Pancreatic cancer represents a major public health related problem, with estimated 44,030 new cases per year and 37,660 deaths in the United States in 2011 [1]. The 5-year relative survival rate for pancreatic cancer is 6%, and if stratified by age groups it varies from 23% in the 15-44 year old group to 4% in the 75-99 year old group [2]. Surgical management with intention to cure is justified whenever an R0 resection can be performed. Interestingly enough, there are some reports showing survival benefit for pancreatic resection and metastasectomy for M1 periampullary cancer of the pancreas in highly selected patients [3], as well as a tendency of increased median survival after surgery in patients with recurrent disease [4].

Godivilla from Italy and Bausch from Germany were the first pioneers in pancreatic resection, while in 1935 the technique of PD (Whipple operation) was modified and described in detail by Whipple et al. [5]. Since then, there have been many modifications of the procedure but currently the pylorus preserving pancreatoduodenectomy (PPPD), described by Traverso and Longmire in 1978, has been adopted by most surgeons [6]. Despite early concerns with delayed gastric emptying after PPPD, large series support no difference between PPPD and classical Whipple operation [7-9].

There is an ongoing debate on whether or not patients requiring technically demanding surgical procedures such as PD should be referred to high volume tertiary centers. Most agree that patients treated in high volume referral centers have better outcomes [10,11], but Hogan and Winter [12] ask "would prognosis be improved if a patient with aggressive disease underwent early intervention at a lower-volume center rather than late intervention at a higher-volume centre?". Meguid et al. [13] suggest that volume cut-off should not be the

Correspondence to: Pavlos Lampropoulos, MD, PhD. 13 Mikras Asias Street GR-16345, Athens, Greece. Tel: +30 210 9949460, Fax: +30 210 4592491, E-mail: pav.lampropoulos@gmail.com

Received 28-08-2011; Accepted 19-09-2011

only criterion as it is not sufficient for defining centers of excellence.

The aim of this study was to report morbidity and mortality rates of patients who had undergone PD for pancreatic cancer at our low volume surgical department in a tertiary institution and to compare our results with others from high volume institutions.

Methods

Patients and surgical procedures

Clinical data and pathology reports were retrieved from "Tzaneio" General Hospital, Piraeus, Greece. A total of 42 unrelated patients, who were surgically treated with PD between 2005 and 2010, were included in this study. No patient had received neoadjuvant chemotherapy or radiotherapy. The study was approved by the hospital review board. Table 1 summarizes the characteristics of the included patients.

Peri-operatively, all patients received i.v. cefoxitin and metronidazole. In cases of documented infection and/or pancreatic fistulae, imipenem/cilastatin combination was used. The use of octreotide was reserved for cases of unsatisfactory pancreatojejunostomy and/or combined soft pancreas and narrow pancreatic duct.

PPPD was our standard technique unless contraindicated or not possible. Three patients had a staging laparoscopy prior to pancreatic resection. All procedures were performed by 4 surgeons. A 2-layer invagination technique with interrupted PDS 4-0 sutures was used for pancreatic anastomosis. Further downstream, an end-to-side hepaticojejunostomy and an antecolic end-to-side duodeno- or side-to-side gastroenterostomy was performed in all cases. Two non-suction surgical drains of penrose type were used in all patients. One of them was placed at the hepaticojejunostomy through a site at the upper right quadrant and the other one was placed at the pancreatoenterostomy through a site at the upper left quadrant. Amylase levels from the drain fluid were measured routinely from post-operative day 5, time at which the drains were removed in uncomplicated cases.

All surgical complications were graded according to the Clavien-Dindo classification (Table 2) [14], while pancreatic specific complications were graded according to the International Study Group on Pancreatic Fistula (ISGPF) and the International Study Group of Pancreatic Surgery (ISGPS) definitions [15,16].

Clinical and pathological information were entered into a database according to the criteria of Tumor-Node-Metastasis (TNM) classification of the International Union Against Cancer [17]. All patients were followed up immediately after discharge from hospital and survival was measured from the date of surgery to the date of death or status at the last follow-up until July 2011. Patients who failed to appear from scheduled appointments during follow-up or died from other causes unrelated to cancer were censored and excluded from further study. Surgical mortality was defined as death in hospital or within 30 days from surgery.

Statistical considerations

All statistical analyses and graphs were performed using MedCalc version 11.5.1.0 (www.medcalc.be) for Windows. Kaplan-Meier survival curves were constructed and differences in survival between groups were compared using the log-rank test. Survival analysis was carried out by using cancer-specific death as the end point. A p-value of < 0.05 was considered as a limit for inclusion of a variable.

Table 1. Patient and tumor characteristics

Characteristics	*N (%)*
Gender	
Male	27 (64.3)
Female	15 (15.7)
Age at diagnosis (years), mean ± SD	63.9 ± 10.9
<70	31 (73.8)
>70	11 (26.2)
Pathology	
Pancreatic adenocarcinoma	36 (85.7)
Ampullary cancer	4 (9.5)
Distal common bile duct cancer	1 (2.4)
Autoimmune pancreatitis	1 (2.4)
Preoperative biliary drainage	
Yes	23 (54.8)
No	19 (45.2)
Type of operation	
Whipple operation	6 (14.3)
Pylorus-preserving PD	36 (85.7)
Lymph node metastasis	
Yes	20 (47.6)
No	22 (52.4)
TNM stage	
IA	1 (2.4)
IB	9 (21.9)
IIA	11 (26.8)
IIB	18 (43.9)
III	2 (4.9)
IV	0

SD: standard deviation, PD: pancreatoduodenectomy

Results

The mean age of 42 patients at the time of diagnosis was 63.9 years (range 35-82) and the population

Table 2. The Clavien-Dindo classification of surgical complications [14]

Grades	*Definition*
Grade 1	No need for therapeutic intervention other than drugs such as antiemetics, antipyretics, analgesics, diuretics and electrolytes. Wound infections opened at bedside and physiotherapy are included.
Grade 2	Pharmacological treatment required other than the ones included in grade 1. Blood transfusions and total parenteral nutrition are also included.
Grade 3	Surgical, endoscopic or radiological intervention is mandatory with or without general anesthesia.
Grade 4	Life-threatening complications including CNS complications and dialysis requiring ICU admission.
Grade 5	Death

consisted of 27 (64.3%) males and 15 (35.7%) females. In 6 (14.3%) patients a classic Whipple operation was performed while 36 (85.7%) patients had been treated with PPPD. In 23 (54.8%) patients an endoscopic retrograde pancreatocholangiography (ERCP) was performed and a plastic stent was inserted for preoperative biliary drainage.

Among the most common presenting symptoms were jaundice in 24 (57.1%) patients, epigastric pain in 9 (21.4%), and weight loss in 8 (19%). The median length of operation was 360 min (range 300-460) and the median length of postoperative hospital stay was 18.5 days (range 10-92).

Endoscopic ultrasonography (EUS) with fine needle aspiration (FNA) was performed in 11/42 (26.2%) patients and the diagnosis of malignancy was achieved in 8/42 (19%) patients. Preoperative diagnosis was achieved in all patients with ampullary carcinoma.

Histology showed pancreatic adenocarcinoma in 36 (85.7%) patients, in 1 case (2.4%) squamous elements were contained within the cancerous tissue, distal bile duct cancer was found in 1 (2.4%) patient and ampullary cancer in 4 (9.5%). One patient operated for suspected malignancy was proved to have autoimmune pancreatitis. The median number of resected lymph nodes was 12.5 (range 4-30). In 20 (47.6%) patients lymph node metastasis was detected. R0 resection was achieved in 37/41 (90.2%) patients.

The overall post-operative morbidity was 59.5%. Among the most common complications were DGE (23.8%), pancreatic fistula (21.4%), hemorrhage (14.3%), wound infections (11.9%), and biliary leakage (7.1%) (Table 3). All patients were treated conservatively except 2 patients who required a re-laparotomy, one for bleeding and the other for peritoneal lavage and drainage of pancreatic fluid collections. Both patients died in the postoperative period. Another patient also died within 30 days from surgery from hepatic insufficiency. Therefore, the mortality rate in our series was 7.1%.

The median follow-up was 23.5 months (range 1-70) and 23 patients died during the study period. Kaplan-Meier survival curve showed a 2-year survival rate of 45.1% and a median survival of 22 months (Figure 1). There was a significant correlation between survival and TNM stage (p=0.0349), but no correlation between survival and age (p=0.7679), gender (p=0.3413), histopathology (p=0.09) or type of operation (p=0.081). However, the number of our patients is too small to make sufficient statistical comparisons and to identify prognostic factors.

Table 3. Outcomes and complications in 42 patients

Complications	*N (%)*
Wound infections	5 (11.9)
Post-operative pancreatic fistula	9 (21.4)
Delayed gastric emptying	10 (23.8)
Hemorrhage	6 (14.3)
Biliary leak	3 (7.1)
Mortality	3 (7.1)

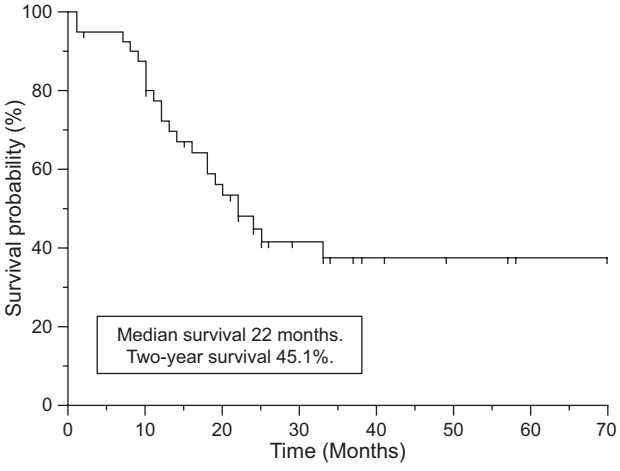

Figure 1. Kaplan-Meier overall survival curve of all patients who underwent pancreatoduodenectomy.

Discussion

PD remains the only chance for increased survival in patients suffering from pancreatic cancer. However, this type of operation is considered as technically challenging, and an increasing number of authors suggest that patients are benefited if treated in high volume centers [18]. Birkmeyer et al. state that high volume institutions offer lower operative mortality and better survival rates compared with low volume institutions [19]. Amongst high volume centers, however, there exists a significant variability in mortality, duration of hospital stay, need for continued nursing care after discharge and cost [20]. Postoperative overall complication rates following pancreatic resection range up to 60%, while postoperative medical complication rates range from 4 to 19% [21]. It is of paramount importance to keep morbidity rates as low as possible, as in cases of re-operation the mortality rate increases up to 67% [21]. Fortunately, most complications can be managed conservatively, computed tomography aided and/or endoscopically.

In our study the overall complication rate was 59.5%. Eight out of 42 patients had a pancreatic fistula type A which was managed conservatively in all cases, no patient had type B fistula, and 1 had developed type

C fistula, making an overall pancreatic fistula rate of 21.4%. Our results are compatible with data from the relevant literature with reports 2-24% pancreatic fistula rate [22]. As mentioned above, drains are removed on post-operative day 5 in uncomplicated cases. In a recent prospective randomized trial [23] patients with low risk for pancreatic fistula (amylase value in drains ≤ 5000 U/L) were randomized to have either early drain (post-operative day 3) or late drain (post-operative day 5) removal. Delayed drain removal had a significant association with increased fistula rate ($p<0.001$) and in multivariate analysis was an independent risk factor ($p=0.0003$). Furthermore, early removal of drains (post-operative day 4) is an independent risk factor for reduced infection rate [24]. Thus, it seems that we should re-evaluate our protocol, towards earlier removal of drains.

In our series there were 6 (14.28%) patients who were complicated with hemorrhage. All but one patient were managed conservatively. One patient presented with late hemorrhage (2nd week) from the anastomosis, and a re-laparotomy was decided. The patient eventually died. Hemorrhage following PD is a well characterized complication and occurs in 1-15% of the patients [22,25]. Reactionary hemorrhage occurs within the first 24 hours and is usually the cause of inadequate coagulation, a slipped ligature, or bleeding from the anastomosis. Immediate re-laparotomy is required in the former case while in the latter case all efforts must be applied to control bleeding conservatively before a decision for re-laparotomy is taken. Delayed hemorrhage (1-3 weeks) has the worst prognosis, and is usually the consequence of anastomotic leak or a pseudoaneurysm [26]. Five of our patients with early hemorrhage were considered to have diffuse oozing due to coagulation defects, thus a conservative approach was decided with aggressive blood transfusions.

DGE was seen in 10 (23.8%) patients. The incidence of this complication is in the range of 19-57% [17]. There is a great deal of articles addressing this topic, and an even more confusion on the precise etiology. Most would agree that the causative factors are decreased motilin concentrations, extended lymph node dissection with autonomic denervation, pylorus defunctioning following PPPD and transient pancreatitis [17]. Yeo et al. reported a reduction in DGE by 37% with the use of intravenous erythromycin [27], while Tani et al. reported that antecolic reconstruction for duodenojejunostomy has better outcome on DGE results, thus reducing morbidity and length of hospital stay in patients following PPPD [28].

Even though, we are able to perform oncologically sound resections, our morbidity and mortality rates remain high compared with reported rates from other series in the literature [17,22,27]. The need for centralization is mandatory in order to reduce morbidity and mortality rates. Careful preoperative investigation, participation of physicians including radiologists, oncologists, gastroenterologists, and pathologists in the decision making and an unbiased discussion at oncology meetings [29] become essential and may further decrease morbidity and mortality.

Our country has failed so far to acquire a centralization policy. Possible explanation for this might be the lack of an accredited hepatopancreatobiliary (HPB) fellowship program, as most surgeons are trained abroad to become HPB certified surgeons. Furthermore, most Greek hospitals lack the multidisciplinary management by different specialists required for such patients. Moreover, Greece has a special geographic distribution which includes some 3,000 islands, which makes referral of patients for quick treatment difficult. Hopefully, in the near future, a new policy will be established to address these issues and provide patients suffering from pancreatic neoplasms with better care and outcome.

References

1. Siegel R, Ward E, Brawley O, Jemal A. Cancer Statistics, 2011: The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011; 61: 212-236.
2. Ellison LF, Wilkins K. An update on cancer survival. Health Rep 2010; 21: 55-60.
3. Seelig SK, Burkert B, Chromik AM, Tannapfel A, Uhl W, Seelig MH. Pancreatic resections for advanced M1-pancreatic carcinoma: the value of synchronous metastasectomy. HPB Surg 2010; 2010: 579672. Epub 2010 Dec 14.
4. Kleeff J, Reiser C, Hinz U et al. Surgery for recurrent pancreatic ductal adenocarcinoma. Ann Surg 2007; 245: 566-572.
5. Whipple AO, Parsons WB, Mullins CR. Treatment of carcinoma of the ampulla of Vater. Ann Surg 1935; 102: 763-779.
6. Traverso LW, Longmire WP Jr. Preservation of the pylorus in pancreaticoduodenectomy. Surg Gynecol Obstet 1978; 146: 959-962.
7. Horstmann O, Markus PM, Ghadimi MB, Becker H. Pylorus preservation has no impact on delayed gastric emptying after pancreatic head resection. Pancreas 2004; 28: 69-74.
8. Di Carlo V, Zerbi A, Balzano G, Corso V. Pylorus-preserving pancreaticoduodenectomy versus conventional Whipple operation. World J Surg 1999; 23: 920-925.
9. Klinkenbijl JH, van der Schelling GP, Hop WC, van Pel R, Bruining HA, Jeekel J. The advantages of pylorus-preserving pancreatoduodenectomy in malignant disease of the pancreas and periampullary region. Ann Surg 1992; 216: 142-145.
10. Mukherjee S, Kocher HM, Hutchins RR, Bhattacharya S, Abraham AT. Impact of hospital volume on outcomes for pancreaticoduodenectomy: a single UK HPB centre experience. Eur J Surg Oncol 2009; 35: 734-738.
11. Ihse I. The association between higher volume and better outcome for pancreatoduodenectomy. HPB (Oxford) 2001; 3:

153-155.
12. Hogan AM, Winter DC. Does practice make perfect? Ann Surg Oncol 2008; 15: 1267-1270.
13. Meguid RA, Ahuja N, Chang DC. What constitutes a "high-volume" hospital for pancreatic resection? J Am Coll Surg 2008; 206: 622. e1-e9.
14. Clavien PA, Barkun J, de Oliveira ML et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009; 250: 187-196.
15. Bassi C, Dervenis C, Butturini G et al. International Study Group on Pancreatic Fistula Definition. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005; 138: 8-13.
16. Wente MN, Bassi C, Dervenis C et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007; 142: 761-768.
17. Sobin LH, Wittenkind C. TNM Classification Of Malignant Tumors (6th Edn). New York: Wiley, International Union Against Cancer, 2002.
18. Sosa JA, Bowman HM, Gordon TA et al. Importance of hospital volume in the overall management of pancreatic cancer. Ann Surg 1998; 228: 429-438.
19. Birkmeyer JD, Sun Y, Wong SL, Stukel TA. Hospital volume and late survival after cancer surgery. Ann Surg 2007; 245: 777-783.
20. Riall TS, Nealon WH, Goodwin JS, Townsend CM Jr, Freeman JL. Outcomes following pancreatic resection: variability among high-volume providers. Surgery 2008; 144: 133-140.
21. Halloran CM, Ghaneh P, Bosonnet L, Hartley MN, Sutton R, Neoptolemos JP. Complications of pancreatic cancer resection. Dig Surg 2002; 19: 138-146.
22. Alexakis N, Halloran C, Raraty M, Ghaneh P, Sutton R, Neoptolemos JP. Current standards of surgery for pancreatic cancer. Br J Surg 2004; 91: 1410-1427.
23. Bassi C, Molinari E, Malleo G et al. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. Ann Surg 2010; 252: 207-214.
24. Kawai M, Tani M, Terasawa et al. Early removal of prophylactic drains reduces the risk of intra-abdominal infections in patients with pancreatic head resection: prospective study for 104 consecutive patients. Ann Surg 2006; 244: 1-7.
25. Schäfer M, Müllhaupt B, Clavien PA. Evidence-based pancreatic head resection for pancreatic cancer and chronic pancreatitis. Ann Surg 2002; 236: 137-148.
26. Friess H, Ho CK, Büchler KJ. Pancreaticoduodenectomy, Distal Pancreatectomy, Segmental Pancreatectomy, Total Pancreatectomy, and Transduodenal Resection of the Papilla of Vater. In: Blumgart LH (Ed): Surgery of the liver, biliary tract, and pancreas (4th Edn). Saunders, Philadelphia, 2007, pp 877-900.
27. Yeo CJ, Barry MK, Sauter PK et al. Erythromycin accelerates gastric emptying after pancreaticoduodenectomy. A prospective, randomized, placebo-controlled trial. Ann Surg 1993; 218: 229-237; discussion 237-238.
28. Tani M, Terasawa H, Kawai M et al. Improvement of delayed gastric emptying in pylorus-preserving pancreaticoduodenectomy: results of a prospective, randomized, controlled trial. Ann Surg 2006; 243: 316-320.
29. Samra JS, Bachmann RA, Choi J et al. One hundred and seventy-eight consecutive pancreatoduodenectomies without mortality: role of the multidisciplinary approach. Hepatobil Pancreat Dis Int 2011; 10: 415-421.