

ORIGINAL ARTICLE

Aggressive Multi-Visceral Pancreatic Resections for Locally Advanced Neuroendocrine Tumours. Is It Worth It?

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ABSTRACT

Context Traditional surgical principles state that pancreatic resection should not be contemplated when malignancies arise in the pancreas and involve other organs. While this is logic for ductal adenocarcinoma and other tumours with aggressive biological behavior; for even large neuroendocrine tumours, aggressive multivisceral resection may achieve useful palliation and excellent survival. **Design** Case records were retrospectively analyzed. **Patients and interventions** Twelve consecutive patients (7 males, 5 females; median age 57 years, range: 37-79 years) underwent multi-visceral en bloc resections for neuroendocrine tumour arising in the pancreas between 1994 and 2008. **Results** Three patients underwent pancreaticoduodenectomy; 9 patients had left sided pancreatic resections for neuroendocrine tumour of median diameter 9.5 cm (5-25 cm). They had a median of 3 (range: 1-4) additional organs resected. There were no post-operative deaths or late mortality with median follow up of 24 months. Five patients experienced a complication (major in 3 patients). Median disease free survival was not attained and 3 patients experienced recurrent disease mostly in the liver and may be candidates for further resection. **Conclusion** Aggressive multi-visceral resection for locally advanced neuroendocrine tumour involving the pancreas is technically feasible and in selected patients can be achieved with low mortality and acceptable morbidity, offering good disease free and overall survival. However this complex surgery should be only performed in specialist centers.

INTRODUCTION

Pancreatic resection for tumours involving the pancreas is still considered a complex and challenging intra-abdominal surgical procedure requiring advanced technical and surgical skills as well as a high standard of pre and post-operative care. In the last two decades thanks to advances in anaesthesia, improvements in surgical techniques and postoperative care, the mortality rate has decreased to less than 5% [1, 2]. However, operative morbidity is still high with incidence reaching 50% in some series [2, 3, 4]. Traditional surgical teaching states that pancreatic

resection should not be contemplated when pancreatic malignancies involve other organs, such that multi-visceral resection would be required to remove the tumour. While this may be true for pancreatic ductal adenocarcinoma and other tumours with an aggressive growth pattern, for pancreatic neuroendocrine tumours aggressive surgical resections may achieve useful palliation [5] and excellent survival has been demonstrated with smaller locally advanced tumours [6, 7, 8, 9, 10]. Furthermore, such tumours often respond poorly to other treatment modalities [11], leaving surgery as the only option for treatment. Neuroendocrine tumours are often expected to grow slowly but between a third and a half of patients can experience aggressive local spread and metastases with associated debilitating symptoms and a poor outcome (20% 5-year survival for pancreatic neuroendocrine tumour metastasizing to the liver for untreated cases [12]). Loco- or chemo-ablative strategies while options for treatment for low volume disease are not as fully developed as for hepatocellular carcinoma and given the different vascular growth patterns of neuroendocrine tumour surgical resection (whether as liver transplantation or multivisceral resection) even in advanced disease may represent the best avenue for

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Table 1. Characteristics of patients and histology for cases with or without recurrence.

Characteristic	Recurrence (n=3)	No recurrence (n=9)	P-value
Median age (range); years	55 (49-73)	57 (36-78)	0.723 ^a
M:F ratio	3:0	4:5	0.204 ^b
Median tumour size (range); cm	20 (8-25)	8 (5-15)	0.250 ^a
Median number of organs resected (range)	4 (2-7)	3 (2-6)	0.600 ^a
Nodal involvement	1 (33.3%)	3 (33.3%)	1.000 ^b
Intravascular invasion	0	2 (22.2%)	1.000 ^b
R0	1 (33.3%)	3 (33.3%)	1.000 ^b

curative intent. Several case series have reported success with locally advanced disease [6].

This study reports a series of cases of multi-visceral resection of large neuroendocrine tumours involving the pancreas at the most aggressive end of the spectrum of possible resections and describes the peri-operative and long term outcomes from these challenging surgical techniques.

METHODS

Twelve consecutive patients who underwent multivisceral resection of abdominal organs for neuroendocrine tumour involving the pancreas between 1994 and 2008 at Southampton General Hospital were identified from theatre records and a surgical database. Multivisceral resection was defined as resection of pancreas and other organs not usually included in standard pancreatic operations, when this was required because of malignancy affecting both the pancreas and the additional organ. In this definition, the duodenum and distal stomach were considered part of a standard pancreaticoduodenectomy, and splenectomy was considered part of left sided pancreatectomy: these organs are not included in the definition of multivisceral resection. The surgical intention was radical resection in all cases. Patient data was entered into a study database, which was analyzed by an independent statistician.

Radiological confirmation of neuroendocrine tumour location and suspected type was sought with ultrasound, barium enema, contrast-enhanced computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP). Upper GI endoscopy, colonoscopy and staging laparoscopy were also performed if required or in cases of radiological doubt. Radiolabelled octreotide scan was used to define the site and functional status. All cases were reviewed at a meeting involving surgeons, radiologists, and pathologists before proposing surgery to patients. All patients were followed up at 3 monthly intervals post-discharge following surgery with clinical review and CT scan. If disease free at 2 years the interval between reviews was lengthened to yearly.

ETHICS

All patients were consented in a two stage process starting in the outpatient setting for all invasive procedures performed. This retrospective analysis

conformed to the standards set out in the World Medical Association Declaration of Helsinki.

STATISTICS

Statistical analysis was performed by using MedCalc (Mariakerke, Belgium; version 9, for Windows XP) and the Statistical Package for the Social Science (SPSS version 12, SPSS Inc., Chicago, IL, USA) software. Survival rates were calculated from date of operation using the Kaplan-Meier method. Comparison of central tendency was performed using the Mann-Whitney U, while categorical variables were compared by using the Fisher's exact test. The study is insufficiently powered to perform logistic regression. Post-operative death was defined as occurring within ninety days of operation. Statistical significance was defined at the 95% level.

RESULTS

Demographics

Twelve patients (7 men, 5 women; median age 57 years, range: 37-79 years) underwent multi-visceral en bloc resections including the pancreas. Three consultant hepatobiliary pancreatic surgeons (MAH, CDJ, NWP) were involved in their care.

Operative Data

Three patients had resection of the pancreatic head by a standard Whipple's operation; nine had left pancreatectomy and splenectomy. Median operative time was 6 hours (range: 3.0-9.3 hours) with median blood loss 1.1 L (range: 0.2-12 L) and median 3 (range: 1-4) additional organs resected. Median tumour diameter was 9.5 cm (5-25 cm) with adequacy of resection and forms of invasion noted in Table 1. Additional organs resected are denoted in Table 2. The

Table 2. Number of resections where different organs were resected. Splenectomy is considered standard for distal pancreatectomy.

Organ	Number of resections involving this organ
Colon	5
Stomach	4
Liver	4
Kidney	4
Adrenal	5
Small bowel	4



Figure 1. Laparotomy photograph of a large neuroendocrine tumour arising in the tail of the pancreas invading the left kidney, adrenal and splenic flexure prior to resection.

typical en-bloc nature of the resected specimen is demonstrated in Figures 1 and 2.

Complications and Mortality

No post-operative (90 day) deaths occurred in this series and all patients were alive after median follow up of 24 months (4-124 months). Three patients had a major complication (25%); median post operative hospital stay was 13 days (range: 9-40 days) with only a small requirement for postoperative critical care stay (ICU median time: 1 day (range: 0-13 days); high dependency unit median time: 2 days (0-4 days)). Five patients experienced a complication; major in three patients (anastomotic leak, perforated colon and severe haemorrhage post operatively). Nevertheless, no re-laparotomies were required. The site of haemorrhage was identified on CT angiography and controlled with formal visceral angiography and embolization. Both the pancreaticojejunal anastomosis leak and perforated colon did not lead to significant clinical deterioration as drains placed at the time of original laparotomy controlled effluent from both complications. There were 9 minor complications as detailed in Table 3.



Figure 2. Specimen photograph from same case in Figure 1 showing the en-bloc resection.

Table 3. Complications experienced in twelve patients undergoing multivisceral resection including the pancreas for neuroendocrine tumour.

Complication	Number of cases
Patients experiencing complication	5
Major complications:	
- Haemorrhage	1
- Perforated colon	1
- Anastomotic leak	1
- Bile leak	0
- Fistula	0
Minor complications:	
- Pneumonia	2
- Intra-abdominal collection	2
- Pseudomembranous colitis	1
- Urine infection	2
- Ileo-femoral deep venous thrombosis	1
- Paralytic ileus	1
- Wound sepsis	0
Total number of complications	12

Median disease free survival was not attained (Figure 3; the disease free interval was 24 months) and 3 patients experienced recurrence in this series. Recurrence was not associated with tumour size, number of organs resected or margin status of the histological analysis (Table 1).

DISCUSSION

This series demonstrates that multi-visceral resection for even large neuroendocrine tumour involving the pancreas and adjacent organs can be performed safely, with good long term results. Multi-visceral intra-abdominal malignancy without distant metastases presents an intriguing surgical problem. Previously, extensive local spread was a relative contraindication to resection due to the technical demands of surgery, risk of intra- or post-operative complications or death and expected short overall survival with or without surgery. This aggressive approach may increase the risk of mortality and postoperative complications. However recent reports from Japan North America and Europe [8, 9, 10, 11, 12, 13, 14] have demonstrated that good results can be achieved in selected patients

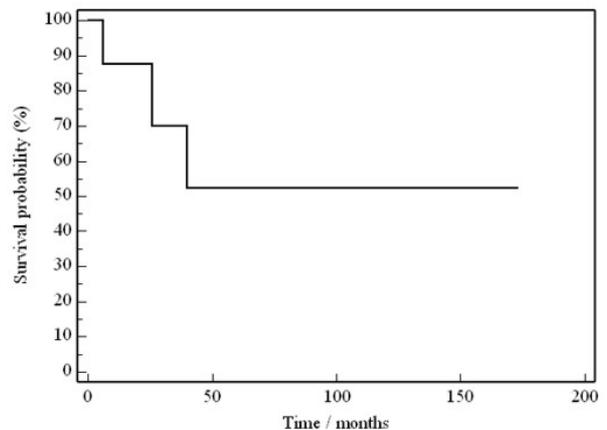


Figure 3. Disease free survival in twelve patients undergoing aggressive multivisceral resection for neuroendocrine tumour involving the pancreas and other organs.

undergoing multi-visceral en bloc resections including the pancreas, suggesting that for extensive local spread; multi-visceral en bloc resection can offer acceptable survival rates without a high risk of early post-operative death [5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16]. Resection of these tumours is desirable to ameliorate mass effects, which can be fatal [6], and to reduce the incidence and severity of debilitating endocrine symptoms.

Patients with large pancreatic neuroendocrine tumours can have excellent symptom control with surgery [15, 16] and can expect a good outcome as in this series, although limited in size, demonstrated no deaths after median follow-up of 20 months. Other recent studies suggest that angio-invasion may be associated with recurrence [6] but we did not observe this in this cohort and, of note, both the previous study and ours note no change in recurrence with size of tumour despite tumour size being significantly larger in our cohort [6]. Disease recurrence is associated with poor outcome and the commonest site for recurrence is the liver. Liver resection can be performed in selected cases [10, 11, 12] and in some cases liver transplantation can be considered with the caveat of the risk of recurrence in the graft. In this series where a median of 3 additional organs were resected this included the liver in 5 cases, and in one a portal vein reconstruction was required in an aggressive resection of 6 additional organs during a distal pancreatectomy. The patient is still alive after 15 months follow-up with recurrence occurring 6 months after surgery. It is not clear from this or other series of aggressive multi-visceral resection of pancreatic neuroendocrine tumour whether there is a ceiling of additional organs where resection is unlikely to provide an additional disease free or overall survival benefit and a larger series would need to be analyzed to define this. Of note the potentially high rate of colonic complications reported by other surgeons [14, 15] was not demonstrated here.

Nevertheless this study has demonstrated that in selected patients, multivisceral resection of neuroendocrine tumours can be performed with low mortality rates by experienced pancreatic surgeons operating in a tertiary referral centre. These resections are followed by good disease-free and overall survival rates. Prospective collaborative studies could help determine optimal surgical strategies of various pathological subtypes and risk factors for recurrence and death in this novel approach to pancreatic surgery.

Conflict of interest The authors have no potential conflicts of interest

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