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ORIGINAL ARTICLE

Results Following Surgical Resection for Malignant Pancreatic Neuroendocrine Tumours. A Single Institutional Experience

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ABSTRACT

Objective The aim of the study was to present clinical outcomes of patients with malignant pancreatic neuroendocrine tumours (NET) following surgical resection with curative intent. Clinical and pathological factors that influenced the outcomes were also analysed.

Design Retrospective case note study.

Patients All patients with pancreatic NET that underwent surgery over a 7-year period (1999-2006).

Results Twelve patients were identified with a median age at diagnosis of 54 years (range: 24-79 years). Common presenting symptoms include abdominal pain (n=8) and weight loss (n=3). Overall morbidity was 25% with one post-operative death. The median follow-up period was 41 months (range: 9-156 months). The overall 2- and 5-year actuarial survival rates were 88% and 70%, respectively. The overall survival was better in patients treated with surgery compared to patients managed medically (P<0.001). The disease-free survival rates were 62% at 2 and 5 years, respectively. Recurrent disease occurred in four patients and the median disease-free interval was 6 months (range: 3-14 months). On univariate analysis, angio-invasion (P=0.015) and degree of differentiation (P=0.024) were associated with developing recurrent disease.

Conclusion Surgical resection of malignant pancreatic NET results in good long-term survival in selected patients.

INTRODUCTION

Neuroendocrine tumours (NET) of the pancreas are relatively uncommon pancreatic tumours with an incidence of approximately 10 per million year [1, 2] and represent 2% to 4% of clinically presenting pancreatic neoplasms [3]. These tumours can be "functional" and exhibit clinical syndromes due to excessive hormone production. Recently, Kloppel *et al*. have refined the classification of NET to improve the correlation between specific pathological findings and post-operative prognosis [4]. This classification is based on defined criteria for benign and malignant NET and includes a category of NET of uncertain malignant potential. It also distinguishes between well and poorly differentiated neuroendocrine carcinomas. With reference to pancreatic NET, each of these categories is subdivided into functional and non-functional tumours.

Due to the highly variable natural history of NET of the pancreas, the management of these neoplasms remains a challenge.

Although the majority of these tumours demonstrate indolent growth patterns, up to 40% of pancreatic NET demonstrate aggressive tumour growth which results in tumour-related deaths [5, 6, 7]. Results following chemo- and radio-therapy have been poor [8] and untreated pancreatic NET with hepatic metastases have a 5-year survival of 20% to 30% [9]. Recent studies have suggested that aggressive surgical resection for pancreatic NET is potentially curative [10, 11] and resection of both the primary tumour and metastatic disease may prolong survival in selected cases [12].

The aim of the current study was to present clinical outcomes of patients with malignant pancreatic NET evaluated at a single institution following surgical resection. In addition, clinical and pathological factors that influenced the outcomes were analysed.

PATIENTS AND METHODS

Patients

Patients who underwent surgery for malignant pancreatic NET from January 1999 to December 2006 were included in a retrospective review of medical, radiological, pathological and surgical reports. Functional tumours were diagnosed by the evidence of clinical symptoms and biochemical analysis of excess hormone production associated with their syndromes. Patients without clinical or biochemical evidence of excess hormone production were diagnosed with non-functional NET even in the presence of immunohistochemical detection of hormone production by the tumour cells.

Pre-operative radiological assessment included a thoracic, abdomen and pelvis computed tomography (CT) and magnetic resonance imaging (MRI) of the pancreas. In selected cases, MRI of the liver was performed if liver metastases or suspicious liver lesions were detected on CT. In addition, an endoscopic ultrasound scan (EUS) and somatostatin receptor scintigraphic scanning (OctreoScan®) were performed in selected cases to further characterise the primary lesion and localise metastatic disease.

Surgery

All surgical procedures were performed with curative intent. Surgical resection with intent to cure involved the complete resection of all tumours identified at operation, including the primary tumour, hepatic metastases and other intra-abdominal disease. Histopathological analysis was based on the WHO classification of pancreatic NET [4].

Follow-up

Following initial post-operative review at 1 month, all patients were examined in the outpatient clinic at 3, 6, 12, 18 and 24 months and annually thereafter. At 3, 6, 12, 18 months, 2 years and annually thereafter CT of chest, abdomen and pelvis was performed. Liver MRI was used to define suspicious lesions demonstrated on CT or in cases of negative CT with recurrence of endocrine-related symptoms.

Outcomes

Clinical outcomes analysed included morbidity, mortality, overall and disease-free survival rates. Mortality was defined as death within the first 30 days post-surgery. Disease-free survival was defined as undetectable tumour recurrence on radiological imaging and the absence of excess hormone production for functioning tumours.

STATISTICS

Continuous data are presented as median and range, and categorical data as both absolute and relative frequencies. The Mann-Whitney and the Fisher's exact tests were applied to assess for a difference in clinicopathological characteristics between patients with recurrent disease and patients that were disease-free following surgical resection with curative intent. The Kaplan-Meier method was used to assess the actuarial survival and disease recurrence rates. All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows™ version 14.0 (SPSS Inc, Chicago, IL, USA), and statistical significance was defined as two-tailed P values less than 0.05.

ETHICS

This is a retrospective study based on the usual clinical practice in accordance with the ethical guidelines of the "World Medical Association Declaration of Helsinki". Informed consent was obtained for all procedures performed in patients in this study.

RESULTS

Demographics

During the study period, 12 of the 26 patients with malignant pancreatic NET underwent surgery with curative intent. The median age at diagnosis was 54 years (range: 24-79) and the male to female ratio was 5:7. The other 14 patients had advanced disease which was not surgically resectable and were managed conservatively.

Frequently reported symptoms at presentation were abdominal pain (n=8, 66.7%) and weight loss (n=3, 25.0%). Nine patients (75.0%) were diagnosed with non-functioning NET. Pancreatic NET were identified incidentally in three patient and two patients had multiple endocrine neoplasia-1 syndrome. The majority of tumours were localised in the head and uncinate process of the pancreas (n=6, 50.0%), followed by the body (n=3, 25.0%) and tail of the pancreas (n=5, 41.7%). There were two patients who had multi-site pancreatic NET and three patients with synchronous hepatic metastases. Pre-operative chromogranin A serum levels were not examined.

Surgery

Curative procedures performed included one total pancreatectomy, 6 pancreaticoduodenectomies (two with portal vein resection and three hepatic resections) and 5 distal pancreatectomies (two with splenectomy and one adrenalectomy and sleeve gastrectomy). Partial or complete control of endocrine-related symptoms was achieved in all patients that had hepatic resection. The total pancreatectomy was performed in one patient with large tumour involving a large proportion of the gland.

The overall morbidity was 25.0% (one post-operative bleeding, one biliary leak and one wound infection). There was one death following post-operative bone marrow failure. The median follow-up period was 41 months (range: 9-156 months).

Histopathology

The majority of resected malignant pancreatic NET in this study was well differentiated (n=9, 75.0%) and the remaining three cases were poorly differentiated. The median size of the pancreatic NET was 3 cm (range: 1-14 cm). There was nodal involvement in eight patients and angio-invasion was present in seven patients. Five patients had evidence of tumour involvement of the posterior circumferential resection margin following surgery. None of the patients had positive transaction margins. Ki-67 immunoreactivity was not performed early on in the series. Five patients did have Ki-67 staining and the median proliferation index was 7.2% (range: 1.8-13.0%).

Outcome and Prognostic Factors Associated with Disease Recurrence

The disease-free survival rates were 62% at 2- and 5-years (Figure 1). The overall 2- and 5-year actuarial survival rates were 91.7% and 73.3%, respectively (Figure 2). Ten patients

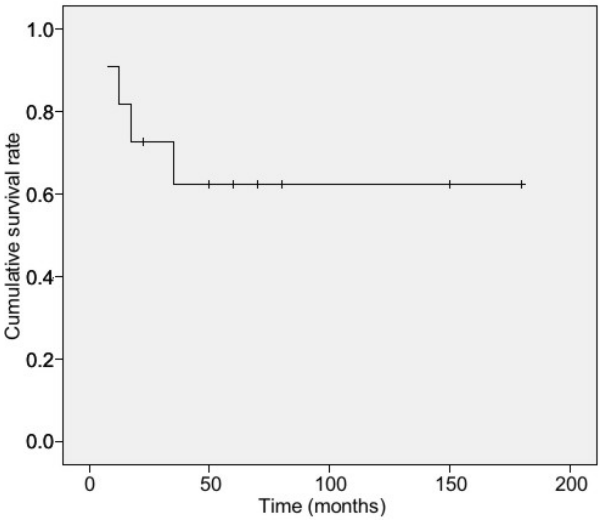

Figure 1. Disease-free survival of patients with pancreatic NET following surgery.

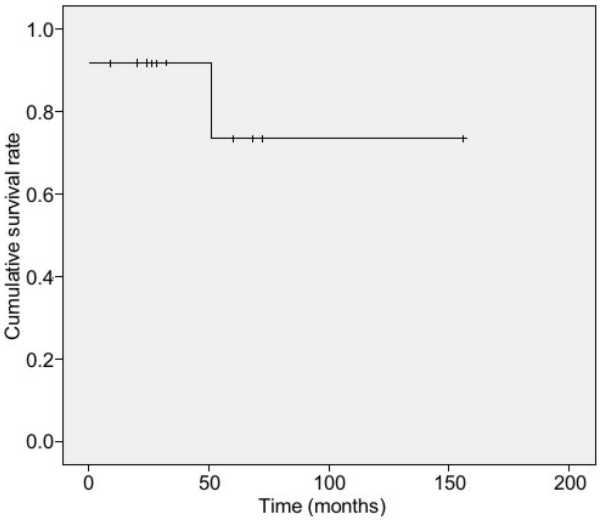

Figure 2. Overall survival of patients with pancreatic NET following surgery.

are still alive and recurrent disease occurred in five sites of four patients: within the remnant pancreas (n=1) and hepatic metastases (n=4). The median disease-free interval was 6 months (range: 3-14 months). Recurrent disease were managed with hepatic transplantation (n=1), hepatic resection (n=3) and resection of the pancreatic remnant (n=1), with three patients currently having stable disease and one patient died at 51 months. The hepatic resections performed included right trisegmentectomy, right trisegmentectomy with left metastectomy, left lateral segmentectomy with right metastasectomies and radiofrequency ablation.

Differences in clinicopathological features of patients who developed recurrent disease are presented in Table 1. On univariate analysis, angio-invasion (P=0.015) and degree of differentiation (P=0.024) were associated with developing recurrent disease.

DISCUSSION

Aggressive surgical resection is the only potential curative approach for patients with pancreatic NET [11, 13] and if left untreated, disease progression leads to hepatic metastasis and death [10]. Fraker *et al*. demonstrated that 23% of patients with gastrinoma who did not have surgery developed hepatic metastasis compared to only 3% in patients who underwent resection of the gastrinoma [14]. Furthermore, in a large series of 163 patients, resection of the primary NET and hepatic metastases conferred significantly better survival [15]. A recent study by Fendrich *et al*. showed that an aggressive surgical policy which included re-

Table 1. Clinicopathological characteristics of patients with pancreatic NET who underwent resection with curative intent. Only 11 patients were included in the statistical analysis due to one post-operative death.

Clinical variables	Recurrent disease (n=4)	Disease-free (n=7)	P value
Age; years [a]	48 (42-58)	58 (24-76)	0.636 [b]
Male:female ratio	2:2	3:4	1.000 [c]
Incidental finding	0	3 (42.9%)	0.236 [c]
Tumour function			1.000 [c]
- Functioning	1 (25.0%)	2 (28.5%)	
- Non-functioning	3 (75.0%)	5 (71.4%)	
Degree of differentiation			0.024 [c]
- Well	1 (25.0%)	7 (100%)	
- Poor	3 (75.0%)	0	
Tumour size; cm [a]	5.0 (1-14)	2.7 (1.7-6)	0.499 [b]
Resection margin involved	3 (75.0%)	1 (14.3%)	0.088 [c]
Angio-invasion	4 (100%)	1 (14.3%)	0.015 [c]
Nodal involvement	4 (100%)	3 (42.9%)	0.194 [c]

[a] Median (range)
[b] Mann-Whitney test
[c] Fisher's exact test

resection of metastatic disease in patients with malignant pancreatic NET led to long-term actuarial survival rates of 81%, 72%, and 36% at 5-, 10-, and 25-years, respectively [16]. In addition to altering disease progression, the elimination of hormonal-induced clinical syndromes following surgery has led to this approach been advocated in various centres [17, 18].

The present study includes 12 cases of pancreatic NET, which according to the WHO classification were malignant and underwent surgery with curative intent [4]. In this study, curative surgery not only included resection of the malignant primary pancreatic tumour but also concurrent resection of synchronous hepatic metastases, as previously done by other groups [16, 19]. Results from the present data showed overall 2- and 5-year survival rates following surgery of 88% and 70%, respectively. The disease-free survival rates were 62% at both 2- and 5-years. Results from the present series are comparable to other studies [16, 20]. Furthermore, compared to patients managed medically, surgically managed patient with NET had a significantly better overall survival. Although limited by a small number of patients, these results indicate that surgical resection in selected patients with pancreatic NET may increase survival.

Various clinical and pathological factors have been shown to determine prognosis following surgery for pancreatic NET. Yu *et al.* showed that a larger primary tumour and the presence of hepatic metastases in patients with gastrinoma were associated with poorer prognosis [6]. Younger patients (less than 50 years) at time of initial surgery have been shown to have better overall survival [16]. Other authors have reported an association with the female gender and an aggressive form of gastrinomas [21]. A recent study by Schurr *et al.* showed that the WHO classification was an independent predictor of disease-free survival [20]. In the present study, only patients with malignant pancreatic NET (based on WHO classification), who underwent curative surgery, were included. On univariate analysis degree of differentiation and angio-invasion were associated with disease recurrence. Although some groups consider poor differentiation as a contraindication to surgery, often the diagnosis can only be made on final histology. We performed aggressive resections in three young patients who had this diagnosis only on final histology. Nevertheless, further larger studies using the WHO classification are required to determine pre- and post-operative predictors of recurrent disease which may help in determining appropriate management strategies.

Disease recurrence following initial surgery is common. In this study, four patients had recurrence; all occurring in the liver and one patient also had recurrence in the pancreatic remnant. One patient was treated with hepatic transplantation and is currently alive although with disease recurrence in the transplanted liver at 72 months. Two patients underwent hepatic resection and are currently disease-free at 15 and 22 months, respectively. One patient underwent repeat pancreatic resection and hepatic resection, but is currently being treated palliatively due to disease progression at 68 months. Although limited by a small sample size, the present series does suggest that resection of recurrent disease may increase survival. Various centres advocate an aggressive surgical policy in performing redo pancreatic and hepatic resections, achieving 5-year survival rates up to 87% [16, 22, 23, 24, 25].

In summary, the present series demonstrates that resection of malignant pancreatic NET results in good long-term survival in selected patients. In addition, in cases of synchronous hepatic metastases or recurrent disease, surgical resection should be attempted.

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Conflict of interest The authors have no potential conflicts of interest

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