Outcomes of 101 Consecutive Surgical Resections of Gastroenteropancreatic Neuroendocrine Tumours (GEPNETs) at Tata Memorial Hospital: a Referral Bias for Nonfunctional Duodenopancreatic Tumours and the Need for Greater Awareness of GEPNETs as a Distinct Entity

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Abstract Data from India regarding the disease spectrum and surgical results of neuroendocrine tumours (GEPNETs) are sparse. Tempered surgical radicality in a high-volume oncology centre, conforming to existing guidelines, may further our understanding of tumour characteristics and behavioural patterns of nonfunctional GEPNETs. Surgical outcomes of patients with histopathologically confirmed GEPNETs from January 2003 to December 2013 were analyzed from a prospectively maintained database. Tumour grade, organ of primary tumour, perioperative factors, quality/radicality of resection and presence of metastatic disease were correlated with perioperative outcomes, overall survival and disease-free survival. Ninety of the 101 operated patients had nonfunctional tumours. These comprised radical resections ($n=69$), organ-preserving procedures ($n=16$) and inoperable tumours ($n=5$). The primary tumour sites were pancreatic in 48 patients and gastroenteric in 42 patients. The overall perioperative morbidity and mortality rates were 30 and 3 %, respectively. Fifteen patients harboured metastatic disease at presentation. At a median follow-up of 22 months, 18 patients had residual disease, 7 developed recurrences and 10 patients died. The estimated actuarial 5-year overall survival was 81.6 %, and disease-free survival was 67.2 %. Tumour grade and organ of origin

(pancreatic vs. gastroenteric) did not influence long-term survival ($p=0.315$ and $p=0.624$, respectively), but presence of metastatic disease at presentation significantly affected long-term survival ($p=0.009$). Nonfunctional pancreatic/duodenal neuroendocrine tumours (NETs) accounted for 76 % of surgical resections at our centre with the minority being other resections. In selected patients with nonfunctional NETs, organ-preserving surgery may provide equivalent long-term survival with decreased operative morbidity. Although tumour grade is considered to be an important prognostic factor, the presence of metastatic disease at presentation also determines long-term survival. The referral bias suggests the need for greater awareness given the favourable long-term outcomes of these tumours. There is a need to correct this referral bias by increasing the awareness of GEPNETs in India.

Keywords Neuroendocrine tumours · Pancreatic neuroendocrine tumours · Duodenal neuroendocrine tumours · India · Surgical outcomes · Gastroenteropancreatic neuroendocrine tumours · Nonfunctional neuroendocrine tumours

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Introduction

The recent institution of the term “gastroenteropancreatic” neuroendocrine tumours (GEPNETs) [1] heralds its appreciation as a separate entity owing to a better understanding of the origin, incidence, specific biological characterization and treatment options of these neoplasms than in the past. The worldwide prevalence of GEPNETs is steadily increasing and is now thought to represent >2 % of all gastrointestinal

malignancies [1, 2]. Greater awareness and improved diagnostic techniques have contributed to the global clinical incidence of 2.5–5 cases/100,000 per year [3]. The vast majority of these tumours are nonfunctional and sporadic [3]. According to the US Surveillance Epidemiology and End Results (SEER) database, a 400 % increase in incidence has been reported over three decades [4].

Classification of neuroendocrine tumours (NETs) is currently based on clinicopathological criteria (WHO 2010) [5]. The categorization into three grades (G1, G2, G3) has aided in the prognostication and reproducibility of classification of these tumours. Based on available literature, the 5-year survival is 96, 73 and 28 % for G1, G2 and G3 tumours, respectively [1, 6]. These results are derived from patients treated surgically as well as nonsurgically and include both functional and nonfunctional tumours which are known to behave differently. Among other factors that are suggested to affect survival are spread of disease at the time of diagnosis, location of the tumour and age of the patient [4].

Very little contributions towards the understanding of these tumours have been derived from out of the USA [7, 8], Europe [9, 10] and East Asia [11, 12]. Surgical data from India regarding NETs are virtually nonexistent [13–15]. While there is general consensus that pancreatic and gastroenteric NETs can be studied under a common umbrella, uncertainty remains whether this heterogeneous group shares characteristics and prognostic similarities that allow for direct comparison [1, 12, 16].

The goal of treatment should be curative whenever possible, which brings surgery to the forefront. Palliative resection also seems justified to improve the quality of life [17]. Which surgical aspects need more specific focus, pertaining to India in particular, can be understood better once we assess concrete surgical data.

This study aims to evaluate outcomes of major surgical resections of GEPNETs referred to Tata Memorial Hospital (TMH), Mumbai, focusing primarily on nonfunctional tumours, to add further information about this yet rare disease group in India.

Patients and Methods

All data were recorded prospectively by the gastrointestinal and hepato-pancreato-biliary (GI and HPB) division of the Department of Surgical Oncology at TMH, Mumbai. The study period extended from January 2003 to December 2013. Patients who underwent surgery with either curative or palliative intent were included in the study.

All treatment decisions were based on an interdisciplinary team approach. The diagnosis of NET was confirmed either preoperatively through biopsy or postoperatively on histopathology. Preoperatively, the diagnosis was made after a biopsy was

performed when NET was suspected on imaging or on routine biopsy performed for diagnostic confirmation. Grading was performed based on the WHO 2010 criteria. For patients who were operated before 2010, reclassification to conform to the current criteria was implemented. A dedicated multidisciplinary team of pathologists performed all pathological reporting.

After 2010, when NET was confirmed preoperatively, a DOTA-D Phe1-Tyr3-Octreotide (DOTA-TOC) scan was performed as the preferred imaging modality. Otherwise, a contrast-enhanced CT scan or a PET scan was performed. Investigations to confirm functionality (serum hormone levels) were performed only if the patient experienced relevant symptoms. A clinical examination to exclude complex cancer syndromes was performed, and a family history was taken in all patients after the diagnosis of NET. Functional tumours were excluded from the final analysis in view of their diverse behavioural pattern, which may hamper the assembly of more valid conclusions.

Preoperative intervention, if carried out, was recorded. Preoperative serum chromogranin (CgA) and 24 urinary 5-hydroxyindoleacetic acid (HIAA) levels were noted if NET was diagnosed preoperatively. Perioperative details such as age, gender and American Society of Anesthesiologists (ASA) score were recorded.

Surgery was planned when curative resection was the goal or when >90 % tumour debulking was predicted to be possible, maintaining an acceptable potential for morbidity and mortality. The operations were carried out or supervised by experienced GI and HPB surgeons. The surgical strategy was based on the anatomical and oncological demand. For localized, well-circumscribed G1 tumours, organ-sparing surgery was performed adopting individually tailored solutions to ensure complete tumour excision. Organ-preserving resections in luminal tumours were performed after endoscopic resection was deemed not possible or insufficient. Radical resections were always oncologic and included a systematic regional lymphadenectomy. Quality of resection was determined according to the R-classification by the International Union Against Cancer (R0=no residual tumour, R1=all identifiable tumour removed, R2=tumour left macroscopically in situ). Intraoperative details including the surgical procedure, blood loss and blood replaced were also recorded. A detailed histopathology report of the resected specimen was documented. Postoperative complications were recorded in accordance with the International Study Group on Pancreatic Surgery (ISGPS) [18, 19] and Center for Disease Control (CDC) [20] guidelines and their management followed.

Patients were followed up at 3-monthly intervals for the first 2 years with serum CgA and imaging (DOTA-TOC/CT/PET scan) and 6-monthly thereafter. The presence of recurrent disease was documented when tumour was detected on follow-up after an initial R0 resection, confirmed by imaging with or without corroboration by increased serum CgA levels.

The patient was deemed to have residual disease when the resection was R1/R2 or if the tumour was inoperable. If follow-up suggested that the patient had died, the cause of death was noted.

The data were analyzed with respect to the primary tumour characteristics, type of operation, short-term outcomes and long-term outcomes. Primary outcome measures were overall survival (OAS) and disease-free survival (DFS), which was measured from the date of surgery till the event. The secondary outcome measure was postoperative morbidity.

The data of the present study were collected in the course of common clinical practice, and accordingly, the signed informed consent was obtained from each patient for any surgical and clinical procedure. The study protocol conforms to the ethical guidelines of the “World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects” adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, as revised in Tokyo 2004.

Survival was calculated adopting the Kaplan-Meier method with 95 % confidence intervals. Variables were explored using the χ^2 test and Fisher exact test. Two-tailed tests were considered significant at a *P* value <0.5. Statistical analyses were performed using the Statistical Product and Service Solutions, SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patient Demography

One hundred one patients, diagnosed with GEPNETs, underwent laparotomy with intent to cure. Eleven patients found to have functional tumours were not included in the study and were investigated based on symptomatic profiling. Eight tumours were insulinomas, and three were gastrinomas (one type II and two type III gastrinomas). One patient with an insulinoma was detected to have multiple endocrine neoplasia I (MEN1) syndrome (parathyroid and pituitary adenomas). The 90 nonfunctional tumours were included in the statistical analysis.

NET was preoperatively confirmed on biopsy in 61 patients, while NET was diagnosed on histopathology of the resected specimen in 29 patients. All patients who had a NET “pathological surprise” along with 40 preoperatively diagnosed patients underwent radical resection in lines with the treatment of adenocarcinoma (*n*=69). Sixteen patients, who had localized G1 tumours, <2 cm in size, underwent organ-preserving procedures. Five patients, all with pancreatic primaries, were deemed inoperable due to locally advanced disease encasing the mesenteric artery.

The median preoperative serum CgA level in preoperatively diagnosed NETs was 56.2 ng/ml (range 2.4–4375 ng/ml). The median urinary 5-HIAA was 6.6 mg/24 h (range 0.71–76.43 mg/24 h) in the same patient subset. Four patients with obstructive jaundice underwent preoperative endoscopic retrograde cholangiopancreatography (ERCP) with plastic stenting.

Surgical Data

The patient profile in relation to the WHO grade is recorded in Table 1. The median age at the time of surgery was 55 years (range 28–73). A statistical significant difference in tumour distribution with regard to grade (G1 vs. G2 vs. G3) when related to patient factors was observed based on gender (*p*=0.041), ASA score (*p*=0.012), radicality of resection (*p*=0.001) and the extent of disease at presentation (*p*=0.024). All R2 resections involved residual metastatic disease and not residual primary disease. Also, in two patients with metastatic disease, metastatectomy was performed for debulking (noncurative) and the resection was therefore documented as R2.

Perioperative Outcomes

Details of the postoperative complications along with the management of the complication with respect to various surgical procedures have been outlined in Table 2. The postoperative morbidity rate was 33 % with three perioperative mortalities. Of the deaths, one patient succumbed to a grade C postoperative pancreatic fistula after a prolonged ICU stay following a pylorus-preserving pancreatoduodenectomy (PPPD), and two patients died due to cardiac failure following a PPPD and a duodenojejunal resection, which could not be salvaged.

The 16 patients who underwent organ-preserving resection had decreased median operative blood loss (200 vs. 600 ml: *p*<0.0001), decreased median operative time (180 vs. 240 min: *p*=0.0015), decreased median hospital stay (4 vs. 7 days: *p*=0.0051) and decreased perioperative complications (2 vs. 28: *p*=0.012) when compared to the 69 patients who underwent radical resection procedures. The median lymph node positivity was zero for both radical and organ-preserving resections.

Survival

Table 3 demonstrates the distribution of patients according to the organ of primary tumour, type and quality of resection, WHO grade, presence of metastasis at presentation and whether metastatectomy was performed and links these parameters to the patient status at last follow-up. At a median follow-up of 22 months, 55 patients were disease free, 18 patients had residual disease, and 7 patients developed recurrent disease. Six patients

Table 1 Patient profile with relation to NET grade (WHO 2010)

Parameter		G1 (n = 50)	G2 (n = 28)	G3 (n = 12)	Total (n = 90)	P value
Age	≤60 years	31	10	7	48	0.172
	>60 years	19	18	5	42	
Gender	Male	22	20	8	50	0.041
	Female	28	8	4	40	
ASA score	I	31	16	9	56	0.012
	II	19	12	3	34	
Radicality of resection	Radical	33	27	9	69	0.001
	Organ preserving	16	0	0	16	
	Inoperable	1	1	3	5	
Resection quality	R0	42	17	9	68	0.174
	R1	3	4	0	7	
	R2	4	6	0	10	
	Inoperable	1	1	3	5	
Organ of origin	Pancreatic	30	10	8	48	0.116
	Gastroenteric	20	18	4	42	
Extent of disease at presentation	Localized	45	18	12	75	0.024
	Metastatic	5	10	0	15	

had disease recurrence in the liver, and one patient had disease recurrence in the retroperitoneal lymph nodes. Ten patients were dead at last follow-up. Three of these were perioperative deaths, and two patients died as a result of cardiac disease. Five patients experienced tumour-related deaths, of which one experienced carcinoid syndrome. Of the five patients who died with disease, two patients had recurrent disease and three patients had residual disease.

Kaplan-Meier curves for OAS and DFS are displayed in Fig. 1. The estimated 5-year OAS was 81.6 %, and the estimated 5-year DFS was 67.2 %.

Figure 2 demonstrates the comparison between DFS of the patients who underwent radical resections and those who underwent organ-preserving resections and also compares the factors that affect survival. The estimated 5-year DFS was 70.4 % for patients who underwent radical resection and 75.8 % for those who underwent organ-preserving resection. The difference was not statistically significant ($p=0.631$).

Only the presence of metastatic disease at presentation was found to be of statistical significance in terms of affecting survival outcome ($p=0.009$). Although the quality of resection (or R status) was shown to be significant prognostic factor on univariate analysis ($p=0.038$), the significance was not demonstrated on multivariate analysis ($p=0.293$). The organ of origin (pancreatic vs. gastroenteric) and tumour grade did not significantly affect survival ($p=0.624$ and $p=0.315$, respectively).

Discussion

Surgical outcomes of GEPNETs in India are lacking. This study now documents the surgical experience of a single

tertiary oncology centre in an area of presumable low endemicity of NETs. Referral bias along with the dearth of data regarding the overall prevalence of these tumours in India certainly poses some limitations regarding the interpretation of this analysis. The relevance, however, increases in the light of the fact that even global data on the surgical management of GEPNETs as a combined entity remains scarce. The intention of covering the entire spectrum of GEPNETs (i.e. pancreatic, gastric and enteric NETs) is not so much for head-on comparison as it is for garnering an essence of the disease profile and prognostic implications.

A number of studies focus on nonsurgical management strategies [21, 22], and some case series involving the surgical treatment of exclusively pancreatic NETs exist [9, 23, 24]. Scattered small series on specific gastric [25] and intestinal NETs [26, 27] also exist. But, these studies do not elaborate on the outcomes of surgically amenable GEPNETs as a collective group and focus predominantly on functional tumours.

What makes GEPNETs unique as a surgical entity is the wide spectrum of radicality that is guided by tumour characteristics. Depending on the size, location, spread and grade of the tumour, surgical radicality can be fine-tuned to minimize operative morbidity. Local excision for small (<1 or <2 cm, depending on the organ of primary), localized and well-differentiated NETs has been advocated, more so when endoscopic resections are not feasible [28]. At the other end of the spectrum, radical resection remains the norm, and aggressive resection of metastatic disease is being encouraged to ensure curative resection or for tumour debulking (>90 % tumour resectable) or even for symptomatic relief [23, 29]. This study underscores the applicability of organ-preserving resections for selected patients with favourable tumour characteristics,

Table 2 Surgical procedures performed based on the site of primary tumour along with perioperative complications and their management

Procedure	N	Primary organ	Complications	Management
PPPD	24	Pancreas (<i>n</i> = 22) Duodenum (<i>n</i> = 2)	POPF A 3 POPF B 6 POPF C 1 {mortality} DGE A 2 SSI 3	Drain prolonged 1 Guided drainage 8 Reexploration 1 Wound care 3 Active observation 5
Whipple	6	Pancreas (<i>n</i> = 2) Duodenum (<i>n</i> = 4)	Local coll 3 POPF A 1 Bleeding C 1	Guided drainage 1 Reexploration 1 Active observation 1
DPS	9	Pancreas	POPF B 2	Drain prolonged 2
Dist pan	3	Pancreas	POPF B 1	Guided drainage 1
Total pan	1	Pancreas	None	NA
<i>Median pan</i>	2	<i>Pancreas</i>	<i>SSI 1</i>	<i>Wound care 1</i>
<i>Enucl</i>	5	<i>Pancreas</i>	<i>Bleeding C 1</i>	<i>Reexploration 1</i>
R hepat	1	Bile duct	Bile leak B 1	Guided drainage 1
Total gas	2	Stomach	None	NA
Prox gas	1	Stomach	None	NA
Dist gas	3	Stomach	None	NA
<i>Ant + duod</i>	4	<i>Stomach (n = 2)</i> <i>Duodenum (n = 2)</i>	<i>None</i>	<i>NA</i>
DJ res	7	Duodenum	Cardiac 1 {mortality}	Cardiology care 1
<i>Excision</i>	3	<i>Duodenum (n = 2)</i> <i>Liver (n = 1)</i>	<i>None</i> <i>None</i>	<i>NA</i> <i>NA</i>
<i>Pan pres duod</i>	2	<i>Duodenum</i>	<i>None</i>	<i>NA</i>
Small bowel RA	4	Jejunum (<i>n</i> = 1) Ileum (<i>n</i> = 3)	None	NA
R hemi	6	Ileum (<i>n</i> = 3) Colon (<i>n</i> = 1) Appendix (<i>n</i> = 2)	SSI 1	Wound care 1
LAR	1	Rectum	Respir 1	Pulmonology care 1
APR	1	Rectum	None	NA
Inop	5	Pancreas	Cardiac 1 {mortality}	NA
Total	90	GEP	30	—

Organ-preserving procedures highlighted in italics

PPPD pylorus-preserving pancreatoduodenectomy, *DPS* distal pancreatectomy, *Dist pan* distal pancreatectomy, *Total pan* total pancreatectomy, *Median pan* median pancreatectomy, *Enucl* enucleation, *R hepat* right hepatectomy, *Total gas* total gastrectomy, *Prox gas* proximal gastrectomy, *Dist gas* distal gastrectomy, *Ant + duod* antrectomy + duodenectomy, *DJ res* duodenojejunal resection, *Pan pres duod* pancreas-preserving duodenectomy, *Small bowel RA* small bowel resection-anastomosis, *R hemi* right hemicolectomy, *LAR* low anterior resection, *APR* abdominoperineal resection, *Inop* inoperable, *POPF* postoperative pancreatic fistula, *DGE* delayed gastric emptying, *SSI* surgical site infection, *Local coll* local collection, *Respir* respiratory, *GEP* gastroenteropancreatic

provided that R0 resection can be ensured, even for nonfunctional tumours. By reducing the radicality of resection, lower perioperative morbidity can be attained while maintaining similar long-term survival. The difference in estimated 5-year DFS between the radical resection and the organ-preserving resection group (70.4 vs. 75.8 %, respectively)

did not attain statistical significance. The potentially superior DFS in the organ-preserving resection group could be attributed to the relatively favourable inherent disease characteristics and not to the decreased radicality of surgery.

This study also questions the routine requirement for lymph nodal clearance, even for radical resections, since the

Table 3 Long-term outcome with distribution of patients according to organ of primary, resection, grade, serum CgA levels and metastatic disease

Organ	N	Resection type			Resection quality				WHO grade			Serum CgA		Mets		Met resection				LFU status (median FU = 22 months)			
		Rad	Org pres	Inop	R0	R1	R2	Inop	1	2	3	y	n	y	n	R0	R+	n	NA	Rec ds	Res ds	Dead	Ds free
Pancreas	48	38	6	5	32	4	7	5	30	10	8	42	6	10	38	4	1	5	38	4	13	7	24
GE	42	31	10	0	36	3	3	0	20	18	4	38	4	5	37	3	1	1	37	3	5	3	31
Duodenum	20	13	7	0	18	0	2	0	9	9	2	18	2	3	17	2	0	1	17	2	1	2	15
Jejunum	1	1	0	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	0	0	1
Ileum	6	6	0	0	5	0	1	0	3	3	0	5	1	2	4	1	1	0	5	0	1	0	5
Appendix	2	2	0	0	2	0	0	0	0	1	1	2	0	0	2	0	0	0	2	0	0	0	2
Colon	1	1	0	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	0	0	1
Rectum	2	2	0	0	0	2	0	0	0	2	0	2	0	0	2	0	0	0	2	0	2	0	0
Stomach	8	6	2	0	7	1	0	0	4	3	1	7	1	0	8	0	0	0	8	1	1	1	5
Liver	1	0	1	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	0	0	1
Bile duct	1	1	0	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	0	0	1
Total	90	69	16	5	68	7	10	5	50	28	12	80	10	15	75	7	2	6	75	7	18	10	55

CgA chromogranin A, *Mets* metastatic disease at presentation, *Met resection* metastasis resection, *LFU* last follow-up, *FU* follow-up, *Rad* radical resection, *Org pres* organ-preserving resection, *Inop* inoperable, *y* yes, *n* no, *NA* not applicable, *Rec ds* recurrent disease, *Res ds* residual disease, *Ds free* disease free, *GE* gastroenteric

median lymph node positivity even for radical surgery was zero. Lymph node involvement may not be as common as previously thought, whatever the grade of tumour.

The study spans across 11 years, and yet, the median follow-up is only 22 months. This reflects the increasing trend of the incidence and/or diagnosis of these tumours. At the

Fig. 1 Overall survival and disease-free survival

Fig. 2 Comparison of disease-free survival between patients who underwent radical resection and those who underwent organ-preserving resections and factors affecting survival in resected nonfunctional GEPNETs

beginning of the study, only two patients were operated per year. This number exponentially increased to 30 patients by the year 2013. The skewed ratio of pancreatic/duodenal NETs to small bowel NETs in this study (76 % pancreatoduodenal tumours) is clearly attributed to referral bias for two reasons. Firstly, TMH is a recognized centre for high-end pancreatic surgery in India [30]. Secondly, the vast majority of conservative gastric and small bowel resections are performed across the country by surgeons in hospitals with varied specialties where guidelines for evaluation and management of NETs are lacking. Availability of guidelines for precise diagnosis, evaluation and treatment would prove invaluable to these surgeons and their histopathologists. The second aspect deserves urgent attention to create better awareness and improve compliance to treatment guidelines for all GEPNETs.

Most previously reported series on pancreatic NETs emphasize WHO tumour grade to significantly affect long-term survival [1, 4]. This observation was not replicated in the present study. Also, there was no difference in survival between pancreatic NETs and gastroenteric NETs. The quality of resection did not significantly affect survival. The factor that did significantly affect survival adversely was the presence of metastatic disease at presentation ($p = 0.008$). The implication is amplified because high-grade tumours (G3) with metastatic disease were not offered surgery and were dealt with in similar lines as those of adenocarcinoma, based on multidisciplinary decision management protocols. It appears that even operable low-grade tumours with metastatic disease have a significantly worse outlook than a localized tumour.

This series, although not a prospective or randomized study, also seems to suggest that amalgamating nonfunctional GEPNETs as a clinical entity seem justified, at least for operable tumours, since both pancreatic and gastroenteric NETs share similar tumour characteristics and portend similar outcomes. This study does not claim to have the power to have practice changing implications, but it might contribute to the

surgical outlook of a tumour group that is rapidly gaining global interest.

We conclude that adhering to existing guidelines, select nonfunctional GEPNETs with favourable tumour characteristics and location should be offered organ-preserving surgery. The presence of metastatic disease at diagnosis appears to be the most important factor in predicting outcomes even for low-grade operable GEPNETs. Lastly, apart from creating greater awareness about the dominant role of surgery in India, this study should serve as a starting point for further multicenter data to emanate from the Indian subcontinent and the Asia-Pacific region.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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