Pancreaticoduodenectomy for non-ampullary duodenal lesions: indications and results

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Authors contribution:
Shamali: Drafting the manuscript, analysing data, and managing the project.
McCrudden: Write paragraph regarding endoscopic management of adenomas, made logarithm for duodenal lesion.
Bhandari: Critical review for the manuscript by expert Endoscopist and Gastroenterologist.
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Introduction

Primary non-ampullary duodenal adenocarcinomas (PDAC) are uncommon tumours characterized by non-specific symptoms and therefore a delayed presentation at diagnosis. PDACs account for just 0.3% of all gastrointestinal malignancies, but represent 25% to 45% of small intestinal adenocarcinomas [1-4]. Two separate carcinogenic pathways of duodenal cancer have been described: the adenoma-carcinoma sequence and the de-novo cancer pathway, both of which are similar to the pathways described in colon malignancies. They may also arise as part of a genetic predisposition such as Familial Adenomatous polyposis (FAP) or Peutz-Jeghers syndrome. Duodenal polyps are uncommon, being reported in 0.3-4.6% of patients who present for Oesophago-Gastro-Duodenoscopy [5]. Management of all duodenal lesions is dependent on a full evaluation of patient's symptoms, clinical features, endoscopic findings, histology and cross sectional imaging. The management of such lesions depends also on patients' fitness for endoscopic resection or surgery. A variety of epithelial and sub-epithelial duodenal lesions exist ranging from lipomas to gastrointestinal stromal tumours (GISTs), neuroendocrine tumours, duodenal adenomas and finally duodenal adenocarcinomas. Historically duodenal adenomas were managed surgically, either by radical resection or by a conservative local excision. More recently renewed interest in advanced endoscopic approaches is emerging. [6]. However, there is no consensus yet regarding which duodenal adenomas should be kept under surveillance and which lesions should be removed either by endoscopy or surgery. [6,7]. Recent results using techniques for endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) show promising results, raising the possibility of duodenal adenoma management through endoscopy rather than the need for radical surgery. This would be an attractive approach for lesions with a low risk of cancer, but more data is required.

The pre-operative histological diagnosis of duodenal lesions is routinely achieved by endoscopic biopsy, followed by cross sectional imaging with surgery indicated when cancer or high grade dysplasia are reported. Complete resection of malignant non-ampullary lesions is the only option for cure. Hence, PD is seen as the only appropriate procedure to achieve complete oncological resection

with adequate lymphadenectomy. PD is a complex procedure, associated with a definite mortality risk and 30-50% complications risk. It is paramount therefore that any surgical intervention is carefully scrutinized. Accurate evaluation of preoperative histology is imperative to guide clinicians in making a definitive plan for surgery given the associated mortality and morbidity. The aim of this study is to assess the outcome of PD in patients with non-ampullary lesions and correlate the preoperative endoscopic, biopsy-related histology to the final histology obtained from the resection specimen.

Materials and methods

An analysis of all PD procedures was undertaken for the period of January 2007 to December 2013. Of the 404 PDs performed at Southampton General Hospital over this 7-year period. Forty patients who underwent PD for primary non-ampullary duodenal lesions were included in our study. All patients underwent a gastroscopy and cross sectional imaging with both abdominal ultrasound and Computerized Tomography (CT) scan of their chest, abdomen and pelvis prior to consideration of surgery. Endoscopic evaluation and tissue acquisition of the lesion was performed in all cases. The individual patient's management was discussed and planned at a multi-disciplinary meeting (MDT) after reviewing endoscopic findings, imaging and histology results. Demographic, clinical and operative data were collected. Macroscopic and microscopic pathologic findings, including size, location, differentiation and nodal involvement of the tumour were analysed. Pre-operative endoscopic histology was compared with final histology to assess the concordance. The pre-operative and the final histology, in the sub-group of patients with low grade dysplasia, have been reviewed by our expert pathologist to confirm the diagnosis. All patients had postoperative peripheral blood tumour markers and a further interval CT scan for surveillance. The pancreatic parenchymal consistency was graded as soft or hard based on intra-operative assessment by the operating surgeon. The hospital length of stay was calculated from the date of operation to the date of discharge, (with both days being inclusive). Complications were graded according to the Clavien-Dindo grading system [8]. Complications such as post-operative pancreatic leak/fistula, delayed gastric emptying and post-pancreatectomy haemorrhage (PPH) were defined according to the International Study Group on Pancreatic Surgery guidelines [9-11]. **Major pancreatic fistula was defined as fistula Grade B or Grade C.** Peri-operative mortality was defined as death due to any cause during hospitalization or within 30 days of surgery. **We compared the peri-operative outcomes of this group of patients with Group B who had a PD for distal CBD lesions and third group (Group C) who had a PD for pancreatic and ampullary lesions.** The seventh edition of American Joint Committee on Cancer (AJCC) classification for malignant neoplasms was used [12].

Statistics

Statistical analyses were carried out using SPSS version 22.0 for Windows statistical package (SPSS Inc., Chicago, IL, USA). Results are reported as mean ±SD and range or frequencies, as appropriate. Two-tailed p-values less than 0.05 were considered to be significant.

Results

Forty patients, (22 females (55%) with a mean age of 69.4 years (range 45-83 years) underwent PD for duodenal lesions. Epigastric pain was the most common presenting symptom (32.5%) followed by anaemia (20%). The majority of these lesions (57.5%) were located in the second part of duodenum, 32.5% were located in the third parte and 4 cases (10%) were located to the first and fourth parts of duodenum. **In our study, the 4 patients who had a lesions involving first and fourth part of the duodenum had tumors extending to the adjacent part of the duodenum (D2 or D3). In addition, all those 4 patients had stage IIIa and stage IIIb adenocarcinoma. Based on this the MDT decision was to perform a Whipple's resection rather than pancreas sparing duodenal resection.**

The most common pre-operative diagnosis was duodenal adenocarcinoma in 23/40 (57.5%), high-grade dysplasia in 12/40 (30%), neuroendocrine tumour (NET) in 2/40 (5%), gastrointestinal stromal tumour (GIST) in 2/40 (5%) and one patient had a metastasis from a caecal cancer (table 1).

Post-operative histology identified: duodenal adenocarcinoma in 26/40 (65%) patients, low-grade dysplasia in 6/40 (15%) cases, high-grade dysplasia in 3/40 patients (7.5%), GIST in 2/40, NET in 2/40 and metastatic caecal cancer in one patient. The average tumour (lesion) size was 36 mm (range 5-103 mm). Lymph node metastasis was present in 19/40 patients, 4 patients had R1 resection. The median length of stay was 15 days (range: 7-66 days). Median survival of all PDAC patients was 26 months.

In the adenocarcinoma group (26 patients), 5/26 (19.2%) tumours were well differentiated and 12/26 (46.2%) were moderately differentiated. The remaining 9/26 (34.6%) tumours were poorly differentiated. The clinical staging was stage I in 2/26 patients, stage IIa in 5/26 patients, stage IIIa 13/26 patients and stage IIIb in 6/26 patients (seventh edition of AJCC classification).

Review of the pre-operative biopsies by our expert pathologist of the patients who had low grade dysplasia on the final histology but reported as HGD on the pre op histology confirmed the presence of low-grade dysplasia in the four cases in which biopsy material was available for review. One of

these biopsies had originally been reported as showing adenoma with predominantly low-grade dysplasia and a focus suspicious for high-grade dysplasia but there was no convincing evidence of HGD on review. Review of the pancreatico-duodenectomy specimens confirmed the presence of low-grade dysplasia in all 6 cases.

The overall complication rate was 55%, the most common complication being pancreatic fistula in 13/40 (32.5%). Pancreatic fistula was Grade A in 3/13 (23.1%), Grade B in 6/13 (46.2%) and in 4 patients (30.7%) Grade C pancreatic fistula was seen. Delayed gastric emptying was observed in five patients (12.5%) and four patients (10%) had post-pancreatectomy haemorrhage. The re-operation rate was 10% (4/40) and 90-day mortality was observed in 2/40 (5%).

There was no significant difference in overall complications between the three groups, but the duodenal group had a significantly higher number of patients who had a major pancreatic fistula, re-operations, and intraabdominal collections, (table 2). In addition, patients with duodenal and CBD lesions had a significant smaller size of pancreatic duct compared to the third group (p=0.025). The incidence of soft pancreas was found to be significantly higher in the duodenal group, 62.5% compared to 42.9% and 34.9% in group B and C respectively, (p=0.0001)

Table 3 shows the correlation between pre-operative histology obtained from endoscopic biopsy with the final histology obtained from post-operative resection specimen. A preoperative diagnosis of cancer, GIST or NET was confirmed on final histology of the resected specimen. However, of the 12 patients with HGD on pre-operative histology, only 3/12 had HGD confirmed after surgical resection. In the remaining 9 patients 6 resection specimens showed LGD and 3/12 showed adenocarcinoma.

Discussion

Duodenal adenocarcinoma is a rare malignancy that accounts for less than 0.5% of gastrointestinal malignancies and where complete resection, where possible, remains the only option for cure, PD is the optimal surgical procedure to achieve this. For tumours located in the first, third, or fourth portions of the duodenum, some authors have reported excellent survival and considerably lower post-operative mortality and morbidity following a limited segmental resection [13, 14]. However, some authors have suggested that all duodenal cancers should be treated by PD, where complete regional lymphadenectomy can be achieved [15, 16].

PD is a complex procedure, associated with a definite mortality risk and 30-50% risk of complications. Recent series from specialized surgical centres have reported mortality rates following PD to be less than 5% [17-20]. However, morbidity rates remain high (30%–60%) [18,21,22]. Postoperative complications can lead to an increased length of hospital stay and treatment cost. Pancreatic fistula continues to be the Achilles' heel of pancreatic surgeons. Most leaks run a benign course, only requiring maintenance of intra-operatively placed drains [23]. However, a pancreatic leak can lead to retroperitoneal sepsis with abscess formation and/or destruction of the surrounding tissues and blood vessels with the potential for severe haemorrhage [24]. Particular risk factors for breakdown of the pancreatic anastomosis are a soft parenchymal texture, small main pancreatic duct in the remnant gland, a high degree of remaining pancreatic exocrine function and anastomotic surgical technique [24]. A soft pancreas and small calibre of main pancreatic duct are commonly encountered in patients with duodenal lesions. In our experience 25/40 (62.5%) were associated with a soft pancreas. Pancreatic fistula was observed in 13 patients (32.5%). Interestingly, the majority of those (77%) were serious leaks (Grade B fistula 46.2% and Grade C 30.8%). This is a significantly high percentage of severe leaks when compared to other reports on PDs for all peri-ampullary lesions where Grade A fistula is more frequent [9].

Similarly, we observed a relatively high rate of re-operation for bleeding and sepsis in this patient group (15%). This was also higher in comparison to our patients undergoing surgery for periampullary lesions 4% of which underwent reoperation, which is similar to the rates reported in the literature, where the incidence has been reported between 2.7% and 10.8% [25-28]. The post-operative mortality was 5%, again, this is significantly higher than our mortality rate for periampullary tumours 2%, confirming the increased risks of morbidity and mortality in this subgroup of patients.

Historically, a histological diagnosis of high grade dysplasia (HGD) on endoscopic biopsy was considered a risk factor for the presence of invasive cancer within the lesion. However, our data demonstrates that in patients with a pre-operative pinch biopsy diagnosis of HGD, 25% have carcinoma in the surgical resection specimen, a further 25% have HGD with the remaining 50% only LGD. As a tertiary centre covering a population of 3.7 million our patients are referred from local hospitals, therefore suggesting that the discrepancy between pre-operative and post-operative histological diagnosis was not associated with an individual pathologist working in one centre. Histological evaluation of specimens from secondary care hospitals can be challenging for a number of reasons. Many would agree that factors such as the size and number of the pre-operative biopsy specimens, and artefacts induced by diathermy or tissue handling can make histological assessment very difficult and lead to sampling variability. In the assessment of patients with Barrett's oesophagus guidelines recommend, that all cases of suspected dysplasia should be reviewed by a second expert gastrointestinal pathologist, with review in a cancer centre if intervention is being considered [29]. Our findings suggest that similar guidelines should be implemented for duodenal lesions in order to avoid an unnecessary aggressive surgical procedure.

On the other hand, recent advances in endoscopic techniques such as high definition endoscopy, chromoendoscopy, electronic imaging, magnifying endoscopy, and endoscopic ultrasound with or

without fine needle aspiration should allow us to make a more accurate pre-operative histological diagnosis. In addition, the advances in endoscopic resection technique such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) may increasingly take on a more important role in the management of these lesions. Whilst a definitive role of EMR and ESD in the management of cancer is yet to be defined, one would speculate that there might be a role for these techniques to strengthen the pre-operative assessment. EMR would give the pathologist a large specimen for assessment. If no cancer is found, then the patient would have had a curative resection with very low morbidity. If cancer is found, the endoscopic treatment would not preclude PD or limited duodenectomy. In addition, EMR would help in determining the depth of invasion within the wall layers and the presence or absence of lymph vascular invasion [30-32], which are important factors to be considered when a surgical option is discussed.

Conclusion

Our study confirms that PD for non-ampullary duodenal lesions is associated with high mortality and morbidity. Histological assessment of specimens obtained at the time of endoscopic assessment can be challenging to interpret and may lead to unnecessary radical surgery with its related morbidity and mortality. Clear guidelines on histological assessment and better use of advances in endoscope resolution and function are essential in reducing this margin of error and ensuring appropriate management of patients with this challenging and rare disease. The development of novel endoscopic resection techniques may offer further therapeutic and diagnostic options, which should be considered.

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Table 1 Clinical features and per-operative out-comes of 40 patients with duodenal lesions.

	N= 40 (%)
Median age, years (range)	69.4 (45-83)
Sex, n (%)	
Male	18 (45)
Female	22 (55)
Clinical presentation, n (%)	
Epigastric pain	13 (32.5)
Anaemia	8 (20)
Anorexia and weight loss	7 (17.5)
Obstructive jaundice	6 (15)
Duodenal obstruction	4 (10)
Incidental finding	5 (12.5)
Location, n (%)	
First part of duodenum	3 (7.5)
Second part of duodenum	23 (57.5)
Third part of duodenum	13 (32.5)
Forth part of duodenum	1 (2.5)
Pre-operative diagnosis, n (%)	
Duodenal adenocarcinoma	23 (57.5)
Duodenal adenoma with HGD*	12 (30)
GIST**	2 (5)
NET***	2 (5)
Metastatic cecal cancer	1 (2.5)
Post-operative complications, n (%)	22 (55)
Pancreatic fistula	13 (32.5)
Grade A	3 (23)
Grade B	6 (46)
Grade C	4/ (31)
Delayed gastric emptying	5 (12.5)
PPH***	4 (10)
Reoperation	6 (15)
30-d mortality, n (%)	2 (5)
Median Length of stay, days (range)	15 (7-66)

* High-grade dysplasia
** Gastrointestinal stromal tumor
*** Neuroendocrine carcinoma
**** Post-operative haemorrhage

Table 2 Operative details and post-operative course in the 3 groups

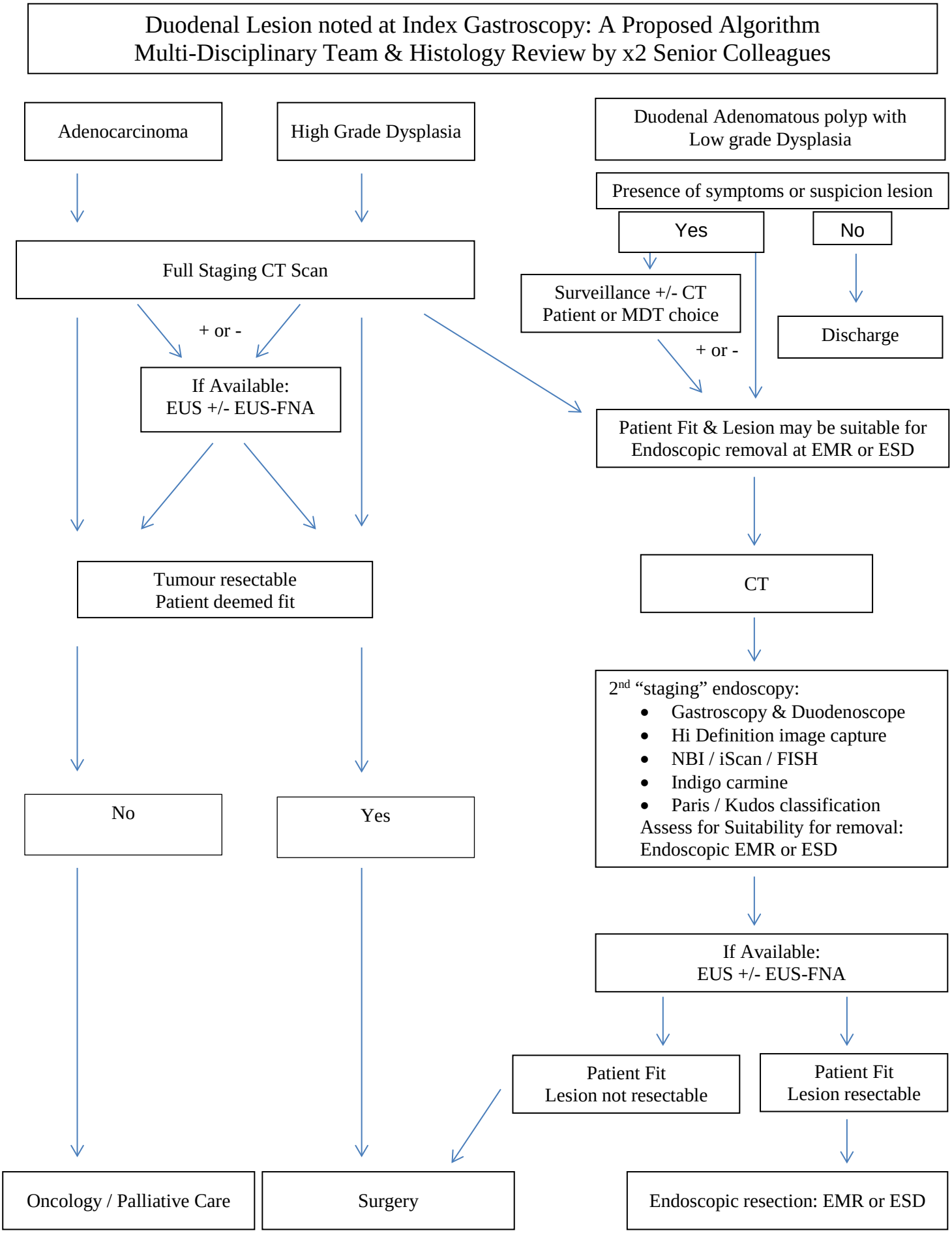
	Group A	Group B	Group C	P value
Numbers	40	35	329	
Gender F/M	22/18	11/24	154/175	0.116
Median age (interquartile range)	69 (63-77)	70 (62-73)	67 (58-73)	0.1
BMI median (interquartile range)	24 (22-30)	25 (23-28)	25 (23-29)	0.863
ASA I ASA II ASA III	6 (15) 33 (82.5) 1 (2.5)	4 (11.4) 28 (80) 3 (8.6)	44 (13.5) 250 (76.1) 43 (10.4)	0.902 0.600 0.266
Presence of soft pancreas	25 (62.5)	15 (42.9)	90 (34.9)	**0.0001**
Median pancreatic duct size (interquartile range)	2 (2-4)	3 (2-4)	4 (2-5)	**0.025**
Median intra-operative blood loss (interquartile range)	500 (300-1000)	600 (400-800)	500 (300-900)	0.776
Operative duration, median (interquartile range)	342 (300-380)	300 (270-400)	360 (300-410)	0.133
Overall complications	22 (55.0)	23 (65.7)	170 (51.7)	0.305
Pancreatic fistula	13 (32.5)	8 (22.9)	59 (17.9)	0.089
Major pancreatic fistula	10 (25)	4 (11.4)	28 (8.5)	**0.006**
Intra-abdominal collection	14 (35)	7 (20.0)	56 (17.0)	**0.007**
PPH	4 (10.0)	5 (14.2)	20 (6.1)	0.051
Re-operation	6 (15.0)	3 (8.6)	13 (4.0)	**0.026**
DGE	5 (12.5)	8 (22.9)	56 (17.0)	0.495
Peri-operative mortality	2 (5.0)	0 (0.0)	7 (2.1)	0.333

Data are presented as absolute number (percentage) unless otherwise indicated PPH=Post-pancreatectomy haemorrhage, DGE Delayed Gastric Emptying, Major pancreatic fistula includes B and C grades.

Table 3 Correlation between preoperative and postoperative histology

Histology	Pre-op histology	Post-op histology	P value*
Cancer	23	26	0.646
Adenoma with HGD	12	3	**0.019**
Adenoma with LGD	0	6	**0.026**
GIST	2	2	1.0
NET	2	2	1.0
Metastatic cecal cancer	1	1	1.0

***** Two-tailed P values less than 0.05 were considered to be significant


Duodenal Lesion noted at Index Gastroscopy: A Proposed Algorithm
Multi-Disciplinary Team & Histology Review by x2 Senior Colleagues
Adenocarcinoma
High Grade Dysplasia
Duodenal Adenomatous polyp with Low grade Dysplasia
Presence of symptoms or suspicion lesion
Yes
No
Full Staging CT Scan
Surveillance +/- CT Patient or MDT choice
Discharge
+ or -
+ or -
If Available: EUS +/- EUS-FNA
Patient Fit & Lesion may be suitable for Endoscopic removal at EMR or ESD
Tumour resectable Patient deemed fit
CT
2nd "staging" endoscopy:
Gastroscopy & Duodenoscope
Hi Definition image capture
NBI / iScan / FISH
Indigo carmine
Paris / Kudos classification
Assess for Suitability for removal: Endoscopic EMR or ESD
No
Yes
If Available: EUS +/- EUS-FNA
Patient Fit Lesion not resectable
Patient Fit Lesion resectable
Oncology / Palliative Care
Surgery
Endoscopic resection: EMR or ESD