Research Article

A 'watch and wait' strategy involving regular endoscopic surveillance is safe for many patients with small sporadic, grade 1, non-ampullary, non-functioning duodenal neuroendocrine tumours.

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Short Title: 'Watch and wait' is safe for many small duodenal neuroendocrine tumours

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Abstract

Introduction

Duodenal neuroendocrine tumours (d-NETs) are rare, but are increasing in incidence. Current ENETS guidelines advocate resection of all localised d-NETs. However, 'watch and wait' may be appropriate for some localised, small, grade 1, non-functioning, non-ampullary d-NETs. We evaluated whether patients with such d-NETs who chose 'watch and wait' involving regular endoscopic surveillance had equivalent disease-related outcomes to patients undergoing endoscopic or surgical resection.

Methods

Retrospective review of patients with histologically confirmed d-NETs at Liverpool ENETS Centre of Excellence 2007-2020.

Results

Sixty-nine patients were diagnosed with d-NET of which fifty were sporadic, non-functioning, non-ampullary tumours. Patient treatment groups were similar in terms of age, gender, tumour location and grade, but unsurprisingly, larger tumours (median diameter 17mm ($p<0.0001$)) were found in the surgically treated group. Five patients underwent surgical resection with no evidence of tumour recurrence or disease-related death. Twelve patients underwent endoscopic resection, with one local recurrence detected during follow-up. Thirty patients (28 with d-NETs ≤10mm) underwent 'watch and wait' with resection only if tumours increased in size. The d-NETs in 28/30 patients remained stable or decreased in size over a median 27 months (IQR:15-48, R:3-98). In seven patients the d-NET was completely removed by avulsion during diagnostic biopsy and was not seen at subsequent endoscopies. Only two patients showed increased d-NET size during surveillance, of whom only one was fit for endoscopic resection. No NET-related deaths were documented during follow up.

Conclusions

All of the localised, ≤10mm, grade 1, non-functioning, non-ampullary d-NETs in this cohort behaved indolently with very low risks of progression and no tumour-related deaths. 'Watch and wait' therefore appears to be a safe alternative management strategy for selected d-NETs.

Introduction

Duodenal neuroendocrine tumours (d-NETs) are a rare type of neuroendocrine cancer with a reported incidence of 2% of all gastrointestinal neuroendocrine tumours [1]. d-NETs are heterogeneous in terms of clinical presentation, histological characteristics and anatomical location and this is reflected by diverse biological behaviour and subsequent prognosis.

Low grade, non-functioning tumours represent up to 60-98% of all d-NETs and this subgroup tends to have a more favourable prognosis[2]. Other functioning d-NETs include gastrinomas; somatostatinomas and gangliocytic paragangliomas while more aggressive poorly differentiated neuroendocrine carcinomas can also occur at this location[3]. Based on their location, d-NETs are categorised into ampullary and non-ampullary. Ampullary d-NETs exhibit more aggressive disease biology and have a different clinical, histological and immunohistochemical profile[4-6].

The most recent ENETS treatment guidelines advocate resection for all d-NETs using either endoscopic or surgical techniques[7]. We recently published a systematic review of the management of localised low grade upper gastrointestinal NETs and found that a few studies had also reported favourable outcomes for patients who had not undergone resection of small, low grade non-functioning, non-ampullary d-NETs[8]. Despite limited follow up data, Burke *at al.* [9]reported 12 patients who did not undergo any treatment with 11 patients being alive after 11 months of mean follow up. More recently, Min *et al.* [10]described 13 d-NET patients who underwent close endoscopic follow up with a mean follow up period of 37 months. Median size of the lesions was 4 mm and 5/13 lesions were unintentionally completely removed using diagnostic forceps biopsy. More importantly, no lymph node or distant metastases developed and no tumour-related deaths occurred during the entire follow-up period.

The types of surgical resection employed for d-NETs, including distal gastrectomy and pancreaticoduodenectomy can be associated with significant morbidity and mortality[11, 12]. Furthermore, endoscopic resection can be complicated by perforation or bleeding[13, 14].

Taking these risks into consideration and the likely favourable prognosis associated with many of these small, localised, grade 1 tumours, 'watch and wait' with regular endoscopic surveillance may be a viable alternative management strategy, especially in patients in whom the risks of surgical or endoscopic resection are increased.

Aim

To perform a retrospective analysis of all patients with non-functioning, non-ampullary d-NETs at our centre to map the natural history of their disease and to evaluate whether patients who had undergone 'watch and wait' involving periodic endoscopic surveillance rather than endoscopic or surgical resection had equivalent disease-related outcomes.

Materials and Methods

Patient selection

All patients diagnosed with a histologically confirmed duodenal neuroendocrine tumour at the Liverpool ENETS Centre of Excellence between February 2007 - 2020 were identified and enrolled in a prospectively collected database. The characterisation of duodenal neuroendocrine tumour was based on the contemporaneous World Health Organisation classification of neuroendocrine tumours. Ethical approval was not required for this retrospective analysis of routinely collected data, but the project was registered and approved by the Audit Department of Liverpool University Hospitals NHS Foundation Trust. Data collected included patient demographics, tumour size, location, histological characteristics, radiological findings, plasma chromogranin A concentration, treatment plan and follow up. All cases were discussed at the NET multidisciplinary team meeting.

Endoscopic assessment and resection

All the patients were endoscopically assessed and followed up by two experienced NET physicians who are also consultant gastroenterologists (~90% of endoscopies performed by DMP and ~10% by ARM) in order to reduce interobserver variability. Polyps were assessed by white light endoscopy assisted by narrow band imaging on each occasion. Tumour size was estimated endoscopically by comparison with an opened pair of biopsy forceps (Single-Use Radial Jaw 4 - Boston Scientific, Hemel Hempstead, UK) and compared with photographss taken at previous endoscopies. Any persistent lesion during follow-up endoscopy was biopsied on each occasion (including scars at the site of previous endoscopic resections). All endoscopic resections were performed by HLS.

Treatment algorithm

Patients who had localised, sporadic, non-functional, non-ampullary d-NETs measuring >10mm diameter were advised to undergo tumour resection, with endoscopic resection being recommended for tumours with a diameter 10-15mm and surgical resection for tumours with a diameter >15mm (Fig.

1). If a patient who had a grade 1 d-NET larger than 10mm or a grade 2 tumour was considered to be unfit for resection due to the presence of significant comorbidities, they were offered surveillance instead. Patients who had small (≤10mm), localised, sporadic, non-functional, non-ampullary d-NETs with a Ki-67 index <3% were counselled regarding the risks and benefits of endoscopic surveillance and endoscopic resection, including the likely indolent course of these tumours, surveillance intervals and rescue strategies if needed. Within this cohort were some patients who had no endoscopic evidence of residual d-NET after initial avulsion using biopsy forceps and they were encouraged to undergo endoscopic surveillance rather than further resection. Patients who had persistent, small d-NETs at follow-up endoscopy and who were considered fit enough for endoscopic resection were counselled regarding the individualised relative risks and benefits of this approach versus endoscopic surveillance, and offered a choice of treatment.

Patients in the endoscopic surveillance cohort underwent annual or biennial oesophago-gastro-duodenoscopy (OGD). For patients undergoing endoscopic treatment, a follow-up examination was performed 4–6 months after the resection procedure. In cases where no residual lesions were found, follow-up examinations were recommended 12 months after the initial procedure and then annually or every two years thereafter. Some patients were not followed up long term due to the presence of severe comorbidities or their choice/non-attendance of appointments.

All patients underwent cross sectional imaging the form of abdominal contrast-enhanced computerised tomography (CT) scan. Nuclear imaging in the form of ^{111}Indium Octreotide scan or more recently ^{68}Ga-DOTATATE PET-CT scan was also undertaken in some patients, particularly when endoscopic or surgical intervention was being considered. Baseline plasma chromogranin A concentrations (normal range <60pmol/L) were measured in all patients.

Statistics

Statistical analysis was performed using GraphPad Prism version 8.4.0 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com. Patient and tumour characteristics were compared between groups using One Way ANOVA with Tukey's correction and Fisher's exact test where appropriate. Differences were considered significant at $p < 0.05$.

Results

Characteristics of entire duodenal NET cohort

In total, 69 patients were diagnosed with a d-NET at our centre over a 13-year period (Fig. 2). Nineteen patients were excluded from further analysis; six patients with ampullary NETs, five patients with

functional d-NETs or associated inherited syndromes such as Multiple Endocrine Neoplasia Type 1 or Neurofibromatosis and eight patients in whom a small d-NET was detected incidentally on histology after they had undergone surgery for an unrelated reason (Supplementary Table 1).

Fifty patients were therefore diagnosed with sporadic, non-functional, non-ampullary d-NETs. Three of these patients did not undergo any follow up endoscopy or treatment due to patient choice, preference for local hospital follow up or because they were unfit for any intervention at the time of diagnosis and they were excluded from our analyses. Five of the remaining 47 patients underwent elective surgical resection based on the size of their tumours, 12 patients underwent planned endoscopic resection and 30 patients were enrolled into an endoscopic surveillance programme. Patient demographics and tumour characteristics are described in Table 1.

There were no statistically significant differences in patient age or gender amongst the three treatment groups. In terms of morphology, most tumours were solitary, located in D1 (90%) and at least 84% were grade 1. Patients undergoing endoscopic surveillance or endoscopic treatment had similar tumour sizes, whereas unsurprisingly the surgical cohort had significantly larger tumours with a median diameter of 17mm (IQR: 15-18mm, $p<0.0001$). Baseline plasma Chromogranin A concentrations were within the normal range in all patients. CT staging did not identify any lymph node or distant metastases at the time of diagnosis. Sixteen patients additionally underwent ^{111}Indium Octreotide scan and twelve had a ^{68}Ga-DOTATATE PET-CT scan. One patient had a somatostatin receptor avid portocaval lymph node, but he was unfit for surgical resection. He therefore underwent endoscopic and CT surveillance with evidence of stable disease for 3 years before he died as a result of one of his other illnesses. A second patient showed evidence of possible tiny somatostatin receptor positive liver metastases, but structural liver lesions were not seen on MR scan and no disease progression was detected on subsequent imaging; his primary tumours also did not increase in size during follow up, his chromogranin A level did not increase and he remains asymptomatic on no treatment six years later. The functional imaging findings in this patient are therefore in retrospect thought to have been artefactual.

Surgery

Five patients underwent a surgical resection with a median tumour diameter of 17 mm (IQR:15-18mm) and median follow up 27.5 months (IQR: 16.4-62.8, R: 10.5-73.7). Peri-operative staging with CT scan and functional imaging did not demonstrate any lymph node or distant metastases in any of these patients. Four of the resected d-NETs were grade 1 and the grade is not available for one patient as surgery was performed prior to referral to our tertiary centre 10 years ago. Four of the patients did not

demonstrate any lymph node metastases on resected specimens, while one patient had N1 nodal involvement. No immediate post-operative complications were noted and no surgical specific related deaths were documented. Two patients have been discharged after 5 years of follow up, two are still under follow-up as their resection was performed more recently and one patient has died and although the cause of death is not definitively known, it is not believed to be d-NET related. No tumour recurrences have been detected in this group.

Endoscopic Resection

Twelve patients underwent endoscopic resection (ER) using a variety of techniques (Table 2). One ER was performed in a patient with a d-NET >10mm in diameter, while 11 were performed in patients with d-NETs ≤10mm who elected to have endoscopic resection rather than 'watch and wait'. Three of these 12 procedures were complicated by perforation; one patient required emergency surgery whereas the other two cases were treated endoscopically with endoscopic clips and intravenous antibiotics. All these rescue measures were successful and there were no procedure related deaths. No significant haemorrhage occurred in any patient. Median follow up for this group was 47 months (IQR:34-66) and patients underwent regular endoscopic follow up with a median of five post EMR surveillance OGDs per patient (IQR:4-5). Eleven patients have shown no evidence of local tumour recurrence. A 4mm tumour was observed in one patient nine months after ER. This patient opted for ongoing endoscopic surveillance and up to four diminutive duodenal polyps have been found during seven subsequent surveillance OGDs over a follow-up period of 72 months . We therefore think that it is most likely that he has developed new d-NETs rather than having a true tumour recurrence. Eight patients have been discharged to date after a median follow up period of 47 months (IQR:41-61, R:13-81) having shown no evidence of residual tumour on follow up surveillance endoscopy or histology. No d-NET related deaths occurred, although two patients have died from unrelated conditions.

Endoscopic Surveillance

The remaining 30 patients were enrolled into a 'watch and wait' endoscopic surveillance programme (Fig. 3, Supplementary table 2). Twenty-seven of these fulfilled the criteria of having ≤10mm diameter and grade 1 d-NETs.Two patients who had grade 2 tumours were also included. One patient who had a 15mm lesion and Ki67% of 4% opted for surveillance as he was synchronously diagnosed with and subsequently died from colorectal cancer and the second patient opted for suveillance because his 5mm, Ki67 8% d-NET was completely avulsed at the time of initial endoscopy. Another patient had a 12mm grade 1 tumour, but he was unfit fior further intervention. All patients underwent at least one surveillance endoscopy with a median of two (IQR:1-4, R:1-7). The time interval from baseline to first

surveillance endoscopy was five months (IQR:3-7) and subsequent endoscopies were performed every 12-15 months. Overall median follow-up was 27 months (IQR:15-48, R:3-98). Seven patients have had only a single follow up endoscopy and a follow up period of less than 12 months. In two cases, endoscopic surveillance was discontinued because these patients were found to also have metastatic colorectal cancer, one older patient was discharged as there was no residual endoscopic abnormality after avulsion of a 2mm d-NET using biopsy forceps, two patients declined the offer of further endoscopic surveillance and two patients are currently awaiting their next surveillance endoscopy, this having been delayed due to the current Covid-19 pandemic.

Seven d-NETs (6 of which measured ≤5mm and including a grade 2 tumour) were unintentionally completely avulsed using diagnostic biopsy forceps at the time of initial endoscopy (most of which were performed outside our tertiary referral centre) with no residual tumour being seen on subsequent endoscopic follow up. This was supported by negative biopsies from the scar site in some cases. None of these tumours have recurred during subsequent follow up and no additional treatment has been required in any of these patients.

Twenty-one of the other 23 tumours have remained stable or have decreased in size over time (median follow up 24 months, IQR:12-46, R:3-98). Three patients did not demonstrate a d-NET on first follow up endoscopy, but diminutive (<5mm) recurrent polyps were found at their 3rd or 4th surveillance endoscopies and have remained stable during subsequent surveillance. Eighteen patients have shown persistent polyps which have not increased in size during follow up. Only two patients were found to have an increase in the size of their lesions during surveillance. The first of these demonstrated an increase from 12mm to 20mm from baseline to first surveillance endoscopy in a time frame of 15 months. He did not fulfil the entry criterion into 'watch and wait' of having a ≤10mm d-NET, but he was not fit for any intervention and has remained under surveillance with no further increase in tumour size being detected over 30 months. The second patient was found to have an increase in tumour size from 10mm at baseline to 13mm at first surveillance endoscopy 20 months later. She therefore underwent an endoscopic resection of a D1, grade 1 lesion with an R0 resection margin (Fig. 3). She has continued under surveillance and there has been no subsequent evidence of endoscopic or histological recurrence.

In addition to the cases described above who have had limited follow up, a further nine patients have been discharged to date from the surveillance programme. These patients either had no residual tumour on follow up endoscopy or had small lesions that remained stable over a median follow-up period of 43 months (IQR:33-52, R:26-98).

Other than the two patients whose baseline functional imaging scans have been discussed above, no patients in this cohort developed confirmed metastatic disease during follow up. Overall, five patients have died (three of these are known to be non-NET related and although the cause of death in two patients is unknown as they died at home or at their local hospital, they are not suspected to be NET related).

Discussion

Duodenal NETs are heterogeneous in terms of histological type, size, secretory status and anatomical location. Patient management plans therefore need to be personalised and take all these features into account. The current ENETS management guidelines recommend resection of all d-NETs, with the mode of resection being influenced largely by the size of the tumour [15, 16, 8]. A recent study by Gamboa *et al* [17] supported this argument as the authors demonstrated improved overall survival with any type of resection regardless of tumour size when compared to no resection. However, although this study included non-functioning d-NETs the authors did not differentiate between ampullary and non-ampullary lesions or take into consideration disease specific survival. Ampullary lesions are recognised as being more aggressive in terms of disease biology and prognosis when compared to non-ampullary d-NETs and surgical resection is therefore advocated for these lesions. In agreement with this, the only known d-NET-related deaths in our cohort occurred in patients who had ampullary tumours.

The incidence of small non-ampullary d-NETs has increased over the last few decades with the advent of widespread diagnostic endoscopy and increased recognition of these lesions[18, 19]. However, reports of the natural history of non-ampullary d-NETs exist in only a handful of case reports and case series[9, 10, 20]. A recent study assessing risk factors for metastases for <20mm non-ampullary lesions identified lymphvascular invasion (LVI), tumour size >11mm and WHO grade 2 as a being risk factors for metastatic disease[21].

It is being increasingly recognised that many non-ampullary d-NETs are detected incidentally and that typical patients are found to have asymptomatic, small, localised, low grade tumours. At our ENETS Centre of Excellence, we were aware of a number of patients who were not fit for endoscopic or surgical resection who showed a very indolent disease course over many years with no evidence of tumour growth, metastasis or d-NET related death. Such d-NETs may therefore have a similar natural history to that associated with small type I gastric NETs, where endoscopic surveillance rather than resection is now the generally recommended management option. We therefore hypothesised that in some cases (namely patients who have localised, ≤10mm diameter, non-functional, grade 1 d-NETs) tumour resection, with its associated risks, can be safely avoided. This option has been proposed for 'early' well

differenciated grade 1 NETs at other sites, namely the stomach, duodenum, rectum and pancreas [19]. Over recent years we have therefore had detailed discussions with such patients about the potential benefits and risks of tumour resection and a number of patients who either have had no evidence of residual d-NET after initial biopsy or who had significant comorbidities or anxieties about potential tumour resection have made an informed choice to have close endoscopic surveillance of their d-NET instead of endoscopic resection. We also offered endoscopic surveillance to two patients who had tumours outwith the selection criteria described above, but who were not fit for elective tumour resection.

In this study, we have reviewed our experience of managing patients who have sporadic, localised, grade 1 , non-functioning, non-ampullary d-NETs and our use of a 'watch and wait' endoscopic surveillance programme as an alternative management strategy in some of these patients. In general, this programme had good compliance and a low attrition rate. The first surveillance endoscopy was usually planned for about 6 months after diagnosis to assess whether any residual duodenal lesion was still present and to assess the rate of growth of any persistent tumour. If the endoscopic appearances were stable, the surveillance interval was subsequently increased incrementally to 12-24 months.We detected a number of patients (7) in whom no residual endoscopic abnormality (other than a scar) was visible after avulsion biopsy of the polyp at the index endoscopy (median tumour size 4mm). None of these tumours recurred locally or at distant sites during subsequent follow up, so the absence of a persistent macroscopic lesion at this stage appears to be a very good prognostic feature. Our observations are therefore similar to those of Min *et al.* for this category of patient. Additional endoscopic resection of the scar site in this type of patient therefore does not appear to be necessary. It is important to note that although avulsion biopsy may successfully treat patients who have <5mm lesions, we do not advocate it as part of the treatment algorithm for d-NETs and formal endoscopic resection remains the gold standard. Over a 13-year period only two of the remaining 23 patients on our surveillance programme who had persistent duodenal lesions demonstrated an increase in the size of their d-NET during follow up. Both increases occurred from baseline to first surveillance OGD and this may have been due to the initial endoscopist at another hospital underestimating the size of the original lesion. Moreover, one of these patients did not fulfil the criterion of having a ≤10mm d-NET at baseline, but he was unfortunately unfit for intervention. Only one of these patients therefore proceeded to endoscopic resection and this was performed successfully. During the entire follow up period, no patients have been found to develop metastases and no known d-NET related deaths have occurred in the 'watch and wait' cohort.

Several patients in our series were either advised or elected to have tumour resection. Our experience using ER demonstrated a complication rate of 25%, which is significantly higher than the complication rate of 8.6% in the systematic review that we recently published. This could be attributed to our small cohort size, but confirms that endoscopic resection of a submucosal tumour at an intestinal site that has a thin wall does have a significant risk of complications. Nonetheless all cases of perforation were successfully salvaged and there were no procedure related deaths. Endoscopic resection was successful in the vast majority of patients (11/12) and no metastases or tumour related deaths were detected in any of these patients during follow up. One patient was found to have a recurrence at nine months after endoscopic resection. This lesion was only 4mm in size and it is distinctly possible that it may represent a new d-NET rather than a recurrence as he has subsequently undergone seven endoscopieds over a period of 72 months and these have demonstrated a number of diminutive d-NETs on each occasion.

We also had good outcomes in our surgical cohort with no significant short-term postoperative complications and again no postoperative tumour recurrences or tumour related deaths. This may be a reflection of our high-volume centre which has minimal morbidity and mortality for such procedures. However, we should not underestimate the long-term morbidity and quality of life in patients undergoing these major operations.

Initial assessment of all patients included measurement of seum chromogrnain A concentration. Baseline chromogranin A levels for were within normal limits in all patients reflecting the modest sesitivity of this test for the diagnosis of small localised non-functioning d-NETs [22]. We did not measure serum Chromogranin A levels as part of the routine follow up of these patients, as several prospective studies have demonstrated that this is not useful [23].

There are no systematic studies of the ability of different modalities to localise duodenal NETs, except in patients with Zollinger Ellison Syndrome[2]. For the vast majority of patients with a duodenal NET who do not have a secretory clinical syndrome, upper gastrointestinal endoscopy is the most sensitive method for tumour detection. We did not perform cross sectional imaging or functional imaging routinely for follow-up in the surveillance group. Almost all patients in this group had a CT scan as part of their initial diagnostic work up and only if there was a clinical concern was this repeated. Although lymph node metastases can occur in small lesions according to Hatta *et al* [21], the main risk factors for metastasis are LVI, tumour size 11-20mm, multiple tumours and grade 2 lesions. Almost all of the patients in our surveillance group did not demonstrate any of these risk factors and the ones who did have been highlighted and discussed. Furthermore, regarding functional imaging, we did not have a

strict protocol for assessing patients with functional imaging modalities unless further intervention was being considered in the form of endoscopic or surgical resection. Some patients in the surveillance group did have functional imaging and this was undertaken on a case by case basis. Factors that contributed to a decision to perform imaging were lesions >10mm, young patient age, patient anxiety and the availability of ^{68}Ga DOTATATE PET/CT scans at our institution at the time.

Our study has some obvious limitations, primarily related to its design. It is a retrospective, single centre, non-randomised study. The surveillance methods for d-NETs include assesment of polyp size which could be deemed subjective. In order to reduce interobserver variability, only two experienced NET gastroenterologists undertook endoscopic assesssment and surveillance of these patients. Additionally, a standardised method of assessement was agreed using biopsy forceps and comparisons were made between images taken at each endoscopy. The median follow up in our surveillance group, is only 27 months as we have included patients who had less than 12 month follow up (e.g. those in whom surveillance has ahd to be postponed due to COVID-19). If those patients are excluded, the follow up period increases to 36 months (IQR: 21-51). We also have to take into consideration that we have safely discharged nine patients who had a much longer follow up period (median 43 months, IQR:33-52, R:26-98). Lastly, when advocating a surveillance programme for d-NETs, life expectancy as well as concurrent comorbiditites should be taken into consideration. A different approach might be appropriate for a fit patient who has been diagnosed in his/her 40s or early 50s when compared to an elderly patient who has significant comorbidities.In conclusion, the prognosis in our series of patients who had localised, small, grade 1, non-ampullary d-NETs and reasonably long follow up was excellent with no confirmed NET-related deaths in the entire cohort. Although those patients who had tumour resection had a good prognosis with no evidence of local tumour recurrence in 16/17 patients, no metastasis and no known tumour related deaths, similar outcomes were also observed in the majority of patients who underwent endoscopic surveillance on the 'watch and wait' programme. Moreover, the d-NETs in the endoscopic resection and endoscopic surveillance groups were of similar small size, with tumours measuring ≤10mm diameter being present in 11/12 and 28/30 cases in these groups respectively. Overall, our observations therefore support an emerging view that many small, sporadic, localised, grade 1, non-ampullary d-NETs have a very indolent disease course.

As some previous papers have reported poor outcomes in a small proportion of d-NET patients, we would still advocate resection of all ampullary d-NETs, all non-ampullary NETs >10mm in diameter and all grade 2 or 3 d-NETs as long as the patient is fit enough to undergo the appropriate procedure. However, as tumour resection can result in various short- and long-term complications, our data suggest that many patients who have ≤10mm sporadic, non-functional, non-ampullary d-NETs,

particularly the majority that are grade 1 can probably be safely managed by a 'watch and wait' strategy We would recommend surveillance initially at 6 months post diagnosis and as long as the lesion is stable then annually for three years and then every two years. Surveillance should be continued for as long as the patient remains fit for either endoscopic and/or surgical intervention. Regading the use of imaging during follow up, we would not advocate routinely performing CT or functional imaging studies unless there is a change in the clinical, endoscopic or histological apprearances. Most patients who are managed in this way appear to require no further intervention and in our series delayed tumour resection in the single patient who demonstrated an increase in d-NET size during follow up did not adversely affect her outcome. A large scale prospective randomised trial would be helpful to validate this approach. However, in view of the rarity of this tumour type, this may be difficult to conduct. We would therefore suggest that at present, it is reasonable to discuss the relative risks and benefits of 'watch and wait' versus endoscopic resection in patients who have sporadic, ≤10mm, non-functional, non-ampullary grade 1 d-NETs and that close endoscopic surveillance with an intention to resect if the tumour increases in size is likely to be a safe management approach in most patients. These criteria can potentially also be extended in terms of tumour size if an individual patient has a substantially increased risk for resection. As patients who undergo endoscopic resection usually also undergo regular endoscopic surveillance for a few years afterwards, this 'watch and wait' strategy is also unlikely to be significantly more expensive. However, a formal economic evaluation of this would be helpful.

Statements

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Statement of Ethics

No ethical approval was required for this retrospective study, but it was approved by the audit department of Liverpool University Hospitals NHS Foundation Trust.

Disclosure Statement

DMP has acted as a consultant for Ipsen, Advanced Accelerator Applications and Laboratoire Mayoly Spindler and has received research funding from Trio Medicines UK. ARM has acted as a consultant for Ipsen. None of the other authors have any conflicts of interest to declare.

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Author Contributions

KE acquisition of data; analysis and interpretation of data; statistical analysis; drafting of the manuscript; critical revision of the manuscript for important intellectual content

ARM analysis and interpretation of data; critical revision of the manuscript for important intellectual content

HLS analysis and interpretation of data; critical revision of the manuscript for important intellectual content

CAD analysis and interpretation of data; critical revision of the manuscript for important intellectual content

NH analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content

DMP study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; study supervision

Figure Legends

Fig. 1. Flow diagram of evaluation and selection criteria for treatment groups of "watch and wait" and endoscopic or surgical resection.

Fig. 2. Flow diagram of all d-NETs diagnoses at Liverpool ENETS CoE between 2007-2020. After initial allocation into treatment groups 42 patients underwent regular endoscopic surveillance. One patient recurred after ER and remained under surveillance and one patient in surveillance required an ER.

Fig. 3. Polyp size on follow up OGDs of patients undergoing endoscopic surveillance. A: Patients that have remained entirely stable over serial OGDs, B: patients in whom d-NETs have reduced in size over time, C: patients whose d-NETs were completely avulsed by biopsy forceps at their initial endoscopy, D: patients demonstrating an increase in d-NET size during follow up.

Table Legends

Table 1: Demographics and tumour characteristics of all non-ampullary non-functioning d-NETs.

Table 2: Patient, tumour characteristics and outcomes of patients undergoing endoscopic treatment.

Supplementary Data

Table 1: Excluded patients from analyses. Demographics, tumour characteristics and outcomes for patients in whom d-NETs were incidental findings, ampullary and functional tumours.

Table 2: Patient and tumour characteristics of all patients undergoing endoscopic surveillance.

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Figure 1

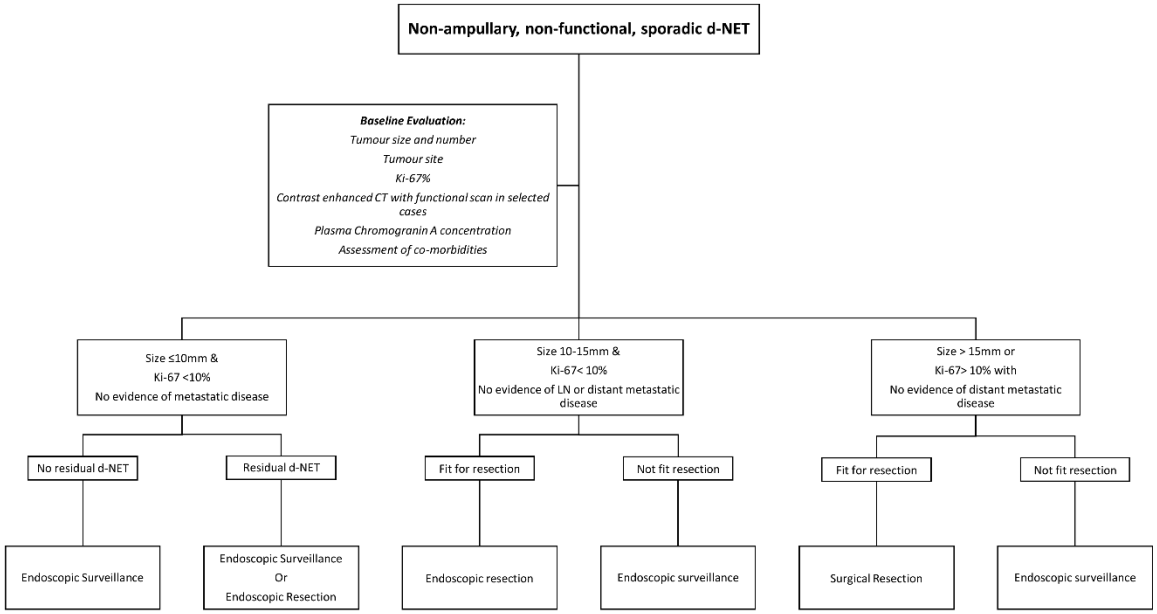
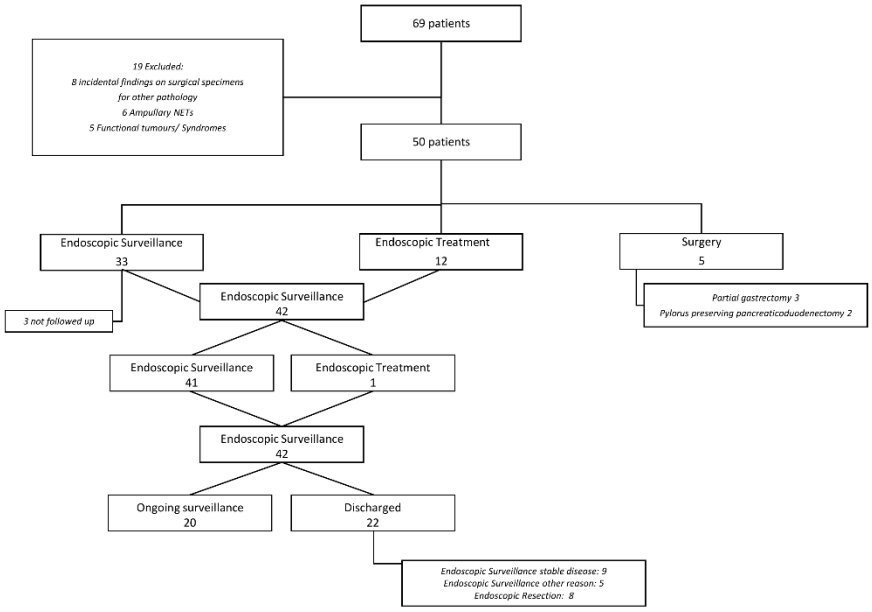

Non-ampullary, non-functional, sporadic d-NET
Baseline Evaluation:
Tumour size and number
Tumour site
Ki-67%
Contrast enhanced CT with functional scan in selected cases
Plasma Chromogranin A concentration
Assessment of co-morbidities
Size ≤10mm &
Ki-67 <10%
No evidence of metastatic disease
Size 10-15mm &
Ki-67< 10%
No evidence of LN or distant metastatic disease
Size > 15mm or
Ki-67> 10% with
No evidence of distant metastatic disease
No residual d-NET
Residual d-NET
Fit for resection
Not fit resection
Fit for resection
Not fit resection
Endoscopic Surveillance
Endoscopic Surveillance
Or
Endoscopic Resection
Endoscopic resection
Endoscopic surveillance
Surgical Resection
Endoscopic surveillance

Figure 2


69 patients
19 Excluded:
8 incidental findings on surgical specimens
for other pathology
6 Ampullary NETs
5 Functional tumours/ Syndromes
50 patients
Endoscopic Surveillance
33
Endoscopic Treatment
12
Surgery
5
3 not followed up
Endoscopic Surveillance
42
Partial gastrectomy 3
Pylorus preserving pancreaticoduodenectomy 2
Endoscopic Surveillance
41
Endoscopic Treatment
1
Endoscopic Surveillance
42
Ongoing surveillance
20
Discharged
22
Endoscopic Surveillance stable disease: 9
Endoscopic Surveillance other reason: 5
Endoscopic Resection: 8

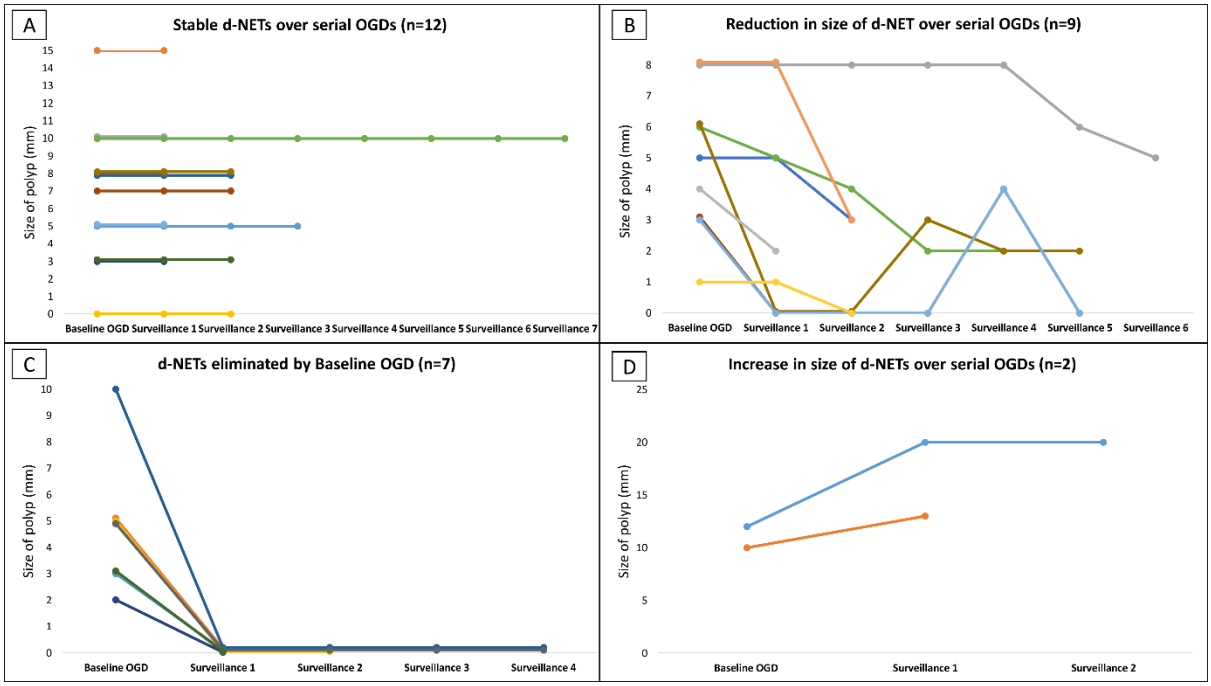

A
Stable d-NETs over serial OGDs (n=12)
Size of polyp (mm)
Baseline OGD Surveillance 1 Surveillance 2 Surveillance 3 Surveillance 4 Surveillance 5 Surveillance 6 Surveillance 7
B
Reduction in size of d-NET over serial OGDs (n=9)
Size of polyp (mm)
Baseline OGD Surveillance 1 Surveillance 2 Surveillance 3 Surveillance 4 Surveillance 5 Surveillance 6
C
d-NETs eliminated by Baseline OGD (n=7)
Size of polyp (mm)
Baseline OGD Surveillance 1 Surveillance 2 Surveillance 3 Surveillance 4
D
Increase in size of d-NETs over serial OGDs (n=2)
Size of polyp (mm)
Baseline OGD Surveillance 1 Surveillance 2

Table 1

	Overall	Endoscopic Surveillance	Endoscopic Treatment	Surgery	p value
n	50	30†	12	5	
Age, years Median IQR	64.5 59.3-71.2	67 59-72.7	61 59.8-66	70 64-74	ns
Sex (%) *Male* *Female*	31 (62) 29 (38)	19 (63) 11 (37)	6 (50) 6 (50)	4 (80) 1 (20)	ns
Solitary lesion *n (%)*	43 (86)	25 (83)	11 (92)	4 (80)	
Size,mm Median IQR	7 5-10	5 3.2-8	6.5 5-9.3	17 15-18	**ES vs S <0.001** **ET vs S <0.001**
Tumour Site D1 D2	45 (90) 5 (10)	28 (83) 2 (7)	11 (92) 1 (8)	4 (80) 1 (20)	ns
Grade G1 G2 G3 UK	43 (84) 2 (4) 0 (0) 5 (10)	26 (86.7) 2 (6.7) 0 (0) 2 (6.7)	11 (92) 0 (0) 0 (0) 1 (8)	4 (80) 0 (0) 0 (0) 1 (20)	ns
Chromogranin A, pmol/l Median IQR	31.5 22-40	32 22-42	30.5 23.8-39.8	18.5 17.3-24.3	ns
Deaths NET related Non-NET related UK	8 0 5 3	5 0 3 2	2 0 2 0	1 0 0 1	-

D1: first part of duodenum; D2: second part of duodenum; UK: unknown; G1: grade 1; G2: grade 2; G3: grade 3; ES: Endoscopic Surveillance; ET: Endoscopic Treatment;
† 3 patients not followed up

Table 2

n	Gender	Age (years)	Location	Technique	Polyp size on baseline OGD (mm)	Size of resected specimen (mm)	Grade (Ki-67%)	Complication	Follow up period from baseline OGD (months)	Local recurrence
1	Female	56	D1	RBL ER	5	5	1 (1)	No	13	No
2	Male	71	D1	RBL ER	5	5	1 (1)	Perforation – surgical management	72	No
3	Female	69	D1	Lift and snare	9	8	1 (1)	No	38	No
4	Male	61	D1	Cap assisted ER	3	3.5	1 (1)	No	82	Yes
5	Female	61	D1	RBL ER	6	6	1 (2)	Perforation-conservative management	42	No
6	Male	61	D1	Cap assisted ER	5	n/a †	n/a †	No	64	No
7	Female	75	D1	RBL ER	7	8	1 (1)	No	49	No
8	Male	51	D1	Lift and snare	10	10	1 (1)	No	81	No
9	Male	60	D1	Lift and snare	15	15	1 (1)	Perforation-conservative management	45	No
10	Female	65	D2	Lift and snare	9	9	1 (1)	No	21	No
11	Male	63	D1	RBL ER	4	4	1 (1)	No	58	No
12	Female	59	D1	Lift and snare	10	8	1 (<1)	No	20	No

D1: first part of duodenum; RBL: Rubber band ligation; ER: endoscopic resection; G1: grade 1;
† Sample not retrieved as removed piecemeal.

Supplementary Data

Table 1

	Incidental finding on surgical specimen	Ampullary NET	Functional tumours
n	8	6	5
Age, years Median IQR	 74.5 69-76	 65.5 47-69	 52 44-68
Sex (%) Male Female	 4 (50) 4 (50)	 3 (50) 3 (50)	 2 (40) 3 (60)
Solitary lesion *n (%)*	 8 (100)	 6 (100)	 3 (60)
Size,mm Median IQR	 2 1.3-5.7	 All lesions >20	 13 10-25
Tumour Site D1 D2 UK	 2 (25) 5 (63) 1 (13)	 0 (0) 6 (100) 0 (0)	 4 (80) 1 (20) 0 (0)
Grade G1 G2 G3 UK	 7 (88) 0 (0) 0 (0) 1 (13)	 3 (50) 0 (0) 3 (50) 0 (0)	 3 (60) 0 (0) 0 (0) 2 (40)
Treatment	Surgery for primary pathology	Surgery: 5 Palliative care:1	Surgery for primary pathology
Primary pathology	Duodenal GIST: 1 Pancreatic cancer: 2 Cholangiocarcinoma: 1 Duodenal adenoma:1 Pancreatic cyst:1 Pancreatic mucinous neoplasm:2	Ampullary NET	Somatostatinoma: 2 MEN1: 2 Neurofibromatosis:1
Outcome	3 deaths from primary pathology	3 deaths due to metastatic NET †	1 death but non-NET related

M: male; F: female; D1: first part of duodenum; D2: second part of duodenum; UK: unknown; G1: grade 1; G2: grade 2; G3: grade 3

† 1 patient was palliative at diagnosis, 2 patients died post-surgery at 10 and 65.4 months respectively

Table 2

Patient	Age at diagnosis	Gender	Follow up period (months)	Follow up OGDs	Site of polyp	Ki-67%	Size at Baseline OGD	Size at Latest OGD	Endoscopically visible lesion at latest endoscopy	Additional Treatment needed
1	62	Male	43	3	D1	2	3	0	No	No
2	73	Male	24	3	D1	Insufficient sample	5	5	Yes	No
3	76	Male	3	1	D1	4	15	15	Yes	No
4	51	Male	7	1	D1	1-2	10	10	Yes	No
5	64	Male	30	2	D2	Insufficient sample	5	0	No	No
6	57	Female	54	4	D1	1	5	0	No	No
7	81	Male	70	6	D1	1	8	5	Yes	No
8	72	Female	15	2	D1	1	5	0	No	No
9	67	Male	21	1	D1	1	1	1	Yes	No
10	71	Male	98	7	D1	1	10	10	Yes	No
11	59	Female	43	2	D1	1	5	3	Yes	No
12	73	Male	59	4	D1	1	6	2	Yes	No
13	52	Male	38	2	D1	1	8	8	Yes	No
14	62	Male	33	4	D1	2	10	0	No	No
15	61	Female	49	5	D1	1	3	0	No	No
16	45	Male	52	5	D1	8	5	0	No	No
17	82	Female	69	5	D1	1	6	2	Yes	No
18	67	Male	28	2	D1	1	7	7	Yes	No
19	68	Male	30	2	D1	<2	12	20	Yes	Not fit for intervention remains under surveillance
20	49	Female	7	1	D2	2	8	8	Yes	No
21	63	Male	20	2	D1	2	8	8	Yes	No
22	74	Female	6	1	D1	1	2	0	No	No

23	49	Female	26	1	D1	<1	3	0	No	No
24	70	Female	20	1	D1	2	10	13	Yes	EMR
25	49	Female	49	5	D1	1	3	0	No	No
26	71	Male	18	2	D1	<2	8	3	Yes	No
27	79	Male	8	1	D1	1	3	3	Yes	No
28	78	Female	15	2	D1	1	2	3	Yes	No
29	59	Male	3	1	D1	1-2	4	2	Yes	No
30	70	Male	4	1	D1	<2	5	5	Yes	No