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What is the appropriate management of non-functioning pancreatic neuroendocrine tumours disclosed on screening in adult patients with multiple endocrine neoplasia type 1?

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Abstract:

Multiple endocrine neoplasia type 1 (MEN1) is an inherited tumour syndrome characterised by a predisposition to the development of endocrine tumours of the parathyroid glands, pituitary and pancreas: 30-80% of patients with MEN1 develop pancreatic neuroendocrine tumours (pNETs), with metastatic tumours and/or their sequelae contributing to increased morbidity and early mortality. The optimal management of non-functioning (NF) pNETs in MEN1 remains controversial. Whilst pancreatic resection is widely recommended for tumours >2cm, for smaller tumours (≤2cm) a well-established consensus guiding the indications for surgical intervention does not exist. Although total pancreatectomy may be curative for some patients, both

short- and long-term complications makes this an unsatisfactory option for many patients. For small (<2cm) MEN1 NF-pNETs, some clinicians advocate surveillance based largely on retrospective data that suggests 50-80% of these lesions are stable over time, and infrequently exhibit accelerated growth rates. It is increasingly recognised, however, that NF-pNETs exhibit unpredictable malignant behaviour that is not determined by tumour size alone, thereby prompting other clinicians to advocate surgery for all MEN1 NF-pNETs, irrespective of size. Such uncertainty poses clinical management challenges with regards to the timing and extent of surgery, which is further hindered by the inability to stratify patients based on predicted tumour behaviour. It is therefore critical that future MEN1 research initiatives include: 1) the discovery of biomarkers that better predict tumour behaviour; 2) the evaluation of medical therapies that may delay, or even prevent, the need for pancreatic surgery; and, ultimately, 3) improvement in the quality of life for individuals with MEN1. Here, based on the published literature, we address the *Clinical Question*, 'What is the management of NF-pNETs disclosed on screening in adult patients with MEN1?'.

What are the current best practice guidelines for the management of NF-pNETs?

There is currently no consensus guidance regarding the management of NF-pNETs in patients with MEN1. **Figure 1** summarises the current recommendations, largely based on consensus expert opinions, published by the *European Neuroendocrine Tumour Society* (ENETS) (1), the *National Comprehensive Cancer Network* (NCCN) (2) and previous guidelines on MEN1 (3). The ENETS and NCCN recommendations essentially relate to non-MEN1 patients.

What is the natural history of MEN1 NF-pNETs?

MEN1 pNETs are typically diagnosed between 30-50 years of age, although marked variability is recognised (4, 5). In contrast, the age of onset of non-MEN1 (sporadic) pNETs usually ranges between 50 and 80 years (6). Similar to sporadic pNETs, MEN-1 pNETs may be either non-functioning or secretory; however, MEN-1 pNETs are typically smaller, occur on a background of diffuse microadenomatosis with a complex

multihormonal expression pattern, and exhibit a more indolent disease course when compared with their sporadic counterparts (7-9). MEN1 patients often have contemporaneous (synchronous) occurrence of multiple tumours in the pancreas, and each one of these independent pancreatic tumours can proliferate and has malignant potential. Although the frequency of the co-occurrence of clinically functioning pNETs and NF-pNETs in MEN1 patients is unknown, pancreata from MEN1 patients with NF-pNETs have been reported to also contain microadenomas immunopositive for insulin, glucagon, pancreatic polypeptide and somatostatin, consistent with the reported complex multihormonal expression pattern (8). Therefore, when considering the most appropriate intervention for NF-pNETs in MEN1, in addition to patient choice, one must also consider the following: i) the risk of malignancy, ii) the risk of developing a secretory tumour, and iii) the risk of new tumour formation. Thus, the risk of disease progression must be measured against the benefit-to-risk ratio of surgery-related morbidity in this young patient population.

Currently, it is not possible to accurately predict the natural history of small (<2cm) MEN1 NF-pNETs. Clinical management strategies that favour early surgical intervention for NF-pNETs in MEN1 are guided by data collated retrospectively that suggests that tumour size correlates with metastatic disease. For example, one study found metastases in 4%, 10%, 18% and 43% of MEN1 patients with NF-pNETs \leq 1cm, 1.1-2cm, 2.1-3cm and >3cm, respectively (10). However, not all studies have confirmed this association (11). It is notable that such studies assume that the largest NF-pNET is the main source of metastases; nevertheless, given the presence of synchronous NF-pNETs in MEN1, it remains possible, indeed likely, that smaller tumours contribute to metastatic disease.

Several studies have confirmed that the majority of small, MEN1 NF-pNETs grow slowly (5, 10, 12). In the Dutch MEN1 study cohort, retrospective analysis of cross-sectional imaging data from 99 patients found that the overall growth rate of small (<2cm) NF-pNETs was 0.4mm per year (median follow-up 3 years) (12). Whilst most patients had stable disease for the duration of the study, in those individuals with progressive tumours (30% of the study population) the growth rate was 1.6mm per year. A recent literature review of seven studies comprising data from 257 patients and 653 NF-pNETs found that tumour growth rates ranged from 0.1 to 1.32mm per year when assessed by conventional

imaging (CT/MRI and EUS) (13). In the same report, pNET incidence rates from five published studies ranged between 0.17 and 1.04 per patient per year (13).

A recent long-term prospective study (follow-up 10.7 + 4.2 years, mean + SD) investigated the outcomes of 46 patients with MEN1 and small (<2cm) NF-pNETs (14) who had not undergone surgery during an earlier three-year study (10). The investigators found that almost two-thirds of patients (60.9%) had one or more NF-pNET <2cm and stable disease over the follow-up period; 39% of patients exhibited progressive disease defined by either an increase in tumour size or the development of a secretory tumour. Of these, seven patients underwent surgery during the study because of an increase in tumour size (>2cm), development of distant metastases or hormone hypersecretion. Three of these patients subsequently developed a new NF-pNET during the study. Only one patient died of metastatic NF-pNET. Of those patients with stable disease for the duration of the study (28/46, 60.8%), the median number of tumours at presentation was 2.3 ± 1.8 per patient compared with 2.9 ± 2.3 tumours per patient at study end.

What is the optimal surveillance modality for early NF-pNETs in MEN1?

The advent of molecular genetic testing and standardised surveillance with sensitive imaging modalities has resulted in the earlier detection of pNETs in patients with MEN1. Indeed, asymptomatic pNETs have been reported in MEN1 patients less than 15 years of age (8, 15), although the largest cohort studies have reported an age-related penetrance for NF-pNETs of less than 10% by 21 years of age (10, 15, 16).

The goals of surveillance for NF-pNETs in hereditary endocrine neoplasia syndromes are to enable early detection and timely intervention to reduce tumour-associated morbidity and mortality. Structured surveillance programmes also serve to reassure gene mutation carriers who have not yet developed a tumour phenotype. However, such programmes may also evoke patient anxiety whilst awaiting test results, and the investigations themselves may have adverse effects. It remains crucial, therefore, that the sensitivity and specificity of a surveillance protocol is balanced with associated risks including radiation exposure (17), affordability and invasiveness.

Current surveillance guidance for MEN1 mutation carriers suggests annual biochemical measurements of fasting gastrointestinal hormones coupled with annual radiological examination of the pancreas and duodenum from around 10-16 years of age (3, 10, 13). However, in the absence of any clinical syndrome the utility of frequently measured gut hormones is debated, as the result rarely alters clinical management. There is no consensus as to the optimal imaging modalities, and conventional methods currently used include cross-sectional imaging (CT, MRI) and/or endoscopic ultrasound (EUS), depending on local availability and expertise. Recent advances in functional imaging and radiopharmaceuticals have also expanded the armamentarium available for the localisation of occult pNETs and the characterisation of tumour burden.

Numerous studies have reported on the relative sensitivity of conventional imaging tests to localise NF-pNETs in MEN1 and, collectively, these data suggest that EUS > CT/MRI > transabdominal ultrasound (4). Owing to availability and affordability, CT is an attractive surveillance imaging test with reported sensitivities of 70-94% for the detection of non-MEN1 and MEN-1 pNETs (18). Specific contrast-enhanced CT protocols are necessary to optimise sensitivity, and more specifically, the timing of contrast enhancement is crucial for the detection of pNETs, as normal pancreatic tissue peak enhancement is delayed in comparison to pNETs (19). However, in patients with MEN1, the benefits of CT must be weighed against the risk associated with lifelong cumulative exposure to ionising radiation in this young and genetically vulnerable patient population (17). It is for this reason that the majority of centres favour MRI. The sensitivity of MRI in localising pNETs in MEN1 is approximately 88%. Furthermore, MRI is more sensitive compared with CT and somatostatin receptor scintigraphy for the detection of hepatic metastases from neuroendocrine tumours (20). However, MRI has limited utility in the detection of tumours <1.2cm (5). Additional limitations of MRI include availability and dependence on patient cooperation, but diffusion-weighted imaging (DWI) sequences improve detection. Of note, emerging evidence has implicated repeated administration of gadolinium-based contrast agents, during contrast enhanced MRI examinations with gadolinium, to be associated with deposition of gadolinium in deep nuclei of the brain, which can be visualised as signal changes on MRI (21). Whilst the clinical significance of centrally-deposited gadolinium is currently unknown, it will be important to monitor this rapidly

evolving research area in order to better understand the long-term implications, if any, for MEN1 patients in whom repeated MRI examinations form the cornerstone of their tumour surveillance strategy.

EUS is the most sensitive imaging modality for the localisation of pNETs. EUS is capable of detecting sub-centimetre tumours as well as identifying incident tumours early in their natural history. In studies that included patients with both sporadic and MEN1 pNETs, EUS was found to have a detection rate of approximately 90% (22), and a sensitivity and specificity of 93% and 95%, respectively (23). In one prospective head-to-head study limited to subjects with MEN1, EUS was superior for the detection of pNETs compared with either CT or MRI when used in isolation or combined with somatostatin receptor scintigraphy (24). However, an earlier prospective study in patients with MEN1 found that EUS and MRI were comparable in the detection of pNETs $\geq 10\text{mm}$ (25). In addition to diagnostic performance, EUS may also facilitate fine needle aspiration of tumour cells thereby enabling tumour grade and other histopathological features to be determined. Limitations of EUS include accessibility, operator dependency, invasiveness and patient acceptability, and reduced sensitivity to detect lesions in the pancreatic tail. It is notable, however, that the clinical value of detecting small ($<1\text{cm}$) non-functional tumours in MEN1 is contentious as their identification is unlikely to alter current approaches in clinical management.

Traditional somatostatin receptor scintigraphy based on, for example, ^{111}In -pentetreotide (*OctreoScan*TM) or $^{99\text{m}}$ -Technetium (*Tecktroyd*), are less sensitive modalities for the detection of pNETs $<1\text{cm}$ (26, 27) compared with conventional modalities, and are associated with reduced specificity owing to physiological uptake in the uncinate process of the pancreas. The recent development of PET/CT using ^{68}Ga -DOTA-labelled somatostatin analogues has demonstrated improved sensitivity in the detection of pNETs, owing to both improved spatial resolution and higher affinity for the somatostatin receptor 2 (sstr2) expressed by NETs. Recent studies have demonstrated that ^{68}Ga -DOTATATE PET/CT is comparable in sensitivity to MRI, and in one study was superior for the detection of sporadic pNETs (28, 29).

In summary, we believe that either EUS or MRI should be considered as part of the first pancreaticoduodenal evaluation in patients with MEN1, in order to thoroughly assess for

the presence of pancreatic lesions and provide histological confirmation of a pNET. On balance, current evidence suggests that subsequent surveillance should be principally based on MRI, however, future studies are required to determine the long-term safety of repetitive gadolinium-based MRI examinations in MEN1 patients and whether non-contrast DWI-MR or EUS are more appropriate surveillance tools.

How useful are current biomarkers at predicting the behaviour and prognosis of NF-pNETs in MEN1?

Circulating biomarkers including chromogranin A (CgA), pancreatic polypeptide (PP), and glucagon, have demonstrated poor diagnostic accuracy for the diagnosis of pNETs in patients with MEN1 (30). The reported sensitivities of CgA for the diagnosis of MEN1 NF-pNETs range between 27% and 70% compared with 36-50% and 43-83% for PP and glucagon, respectively (13). The limited diagnostic performance of these hormonal biomarkers renders them inadequate for the diagnosis, screening and long-term surveillance of MEN1 NF-pNETs.

The WHO tumour grading system has demonstrated prognostic value for both non-MEN1 and MEN1 NF-pNETs, with tumour grade (Grade3 > Grade2 > Grade1) and higher proliferation index both associated with increased risk of metastatic or recurrent disease and overall mortality (31, 32). Notably, the majority of studies which have evaluated the prognostic utility of the WHO tumour grading system have included surgical specimens rather than biopsy specimens (31, 32), and therefore further studies are required to determine whether cytological grading accurately predicts tumour behaviour in both MEN1 and non-MEN1 NF-pNET's.

As mentioned above, functional imaging with somatostatin scintigraphy such as [⁶⁸Ga]-DOTA(0)-Tyr-(3)-octreotate PET/CT (⁶⁸Ga DOTATATE PET/CT) has recognised utility as an adjunct to conventional anatomical imaging for the detection of NF-pNETs and metastatic disease in MEN1 and may identify patients most suitable for treatment with somatostatin analogues and targeted radionuclide therapy. However, it remains unclear as to whether ⁶⁸Ga DOTATATE PET/CT scintigraphy is able to accurately predict the

malignant potential of a NF-pNET (33). In contrast, imaging with ^{18}F -fluorodeoxyglucose PET/CT (^{18}F -FDG PET/CT) has recently been posited as a biomarker with the potential to assess the aggressiveness of MEN1 NF-pNETs (34). ^{18}F -FDG-PET avidity in NF-pNETs has demonstrated a positive correlation with: i) higher proliferation indices (Ki67 > 2%); ii) tumour grade; iii) metastatic potential; and iv) overall survival (35, 36). Importantly, recent data suggests that ^{18}F -FDG-PET avidity can predict tumour aggressiveness in the setting of a low proliferation index (37) and independent of tumour size (34) (**Figures 2A-C**). ^{18}F -FDG-PET avidity does not always predict absence of somatostatin receptor expression, highlighting the potential role for combined imaging using ^{68}Ga -DOTATATE PET/CT and ^{18}F -FDG PET/CT to detect intra- and inter-tumour heterogeneity (38). However, the utility of molecular imaging in clinical practice must be balanced against radiation exposure and cost. Current evidence does not support the routine use of molecular imaging in the initial evaluation or surveillance management of MEN1 NF-pNETs.

Given that a genotype-phenotype correlation has not been established in MEN1, identification of a specific germline *MEN1* mutation currently provides no prognostic value. Whole genome analysis of sporadic pNETs has identified driver somatic mutations in recurring genes affecting four main pathways: i) chromatin remodelling; ii) DNA damage repair; iii) activation of mTOR signalling; and, iv) telomere maintenance (39). Somatic mutations in *MEN1* and the chromatin remodelling genes *ATRX* and *DAXX* have been most commonly reported in sporadic pNETs occurring in non-MEN1 patients (40), and data from integrated analysis has suggested that detection of these somatic mutations may have important prognostic implications (39). For example, loss of function mutations in *DAXX* and *ATRX* may be associated with an increased risk of tumour progression, metastatic disease and a poor prognosis in non-MEN1 patients (39). One small clinical case series has provided proof-of-concept evidence that somatic mutational analysis is possible from DNA obtained by fine needle aspiration (41); however, larger prospective studies are required to determine if somatic mutational analysis may be used to prognosticate for both sporadic and MEN1-associated NF-pNETs.

Recently, the NETest™, a multi-transcript molecular signature for PCR-based blood analysis, has been developed as a biomarker with independent studies reporting variable diagnostic performance in its ability to detect sporadic gastro-pancreatic NETs (42, 43). The NETest™ has also been reported to be able to differentiate stable from progressive sporadic gastro-pancreatic NETs and may have the potential to predict prognosis (44); however additional studies are required to truly establish the clinical utility of the NETest™ in the non-MEN-1 setting. To date, in patients with MEN-1, there are no published data regarding the performance of the NETest™ in the context of MEN1-associated NF-pNETs. It may be anticipated, however, that the NETest™ will have limited utility in the MEN1 population given that the majority of MEN NF-pNETs are small and slow growing, and due to the propensity of these patients to harbour co-existing neuroendocrine tumours that arise from different cellular origins.

What are the treatment options for non-metastatic MEN-1 NF-pNETs?

Surgical excision is the only potentially curative treatment for non-metastatic NF-pNETs in MEN1. The surgical approach offered is dependent on tumour location as well as tumour size, and options include distal pancreatectomy, tumour enucleation, pylorus-preserving pancreaticoduodenectomy, or total pancreatectomy (45). The aims of surgery include prevention of disease progression through complete tumour resection, whilst preserving pancreatic function and avoiding early and late surgical complications such as diabetes mellitus and pancreatic exocrine insufficiency. The main criteria for recommending surgical excision are tumour size and, in some guidelines, tumour growth rate (ie. tumour doubling over a 6-month period). However, the size threshold above which surgery should be undertaken remains contentious. Given the correlation between increased tumour size and presence of liver metastases, surgical resection is recommended for MEN1 NF-pNETs >3cm and probably 2-3cm; however, future clinical studies are required to clearly establish the benefit-to-risk ratio of surgery for the latter tumour subgroup. In MEN1 patients with NF-pNETS ≤2cm data from several studies support a 'watch and wait' approach because most of these tumours have low oncological risk (12, 14, 46). For example, the Dutch MEN1 study group suggested that surgery should be reserved for NF-pNETs >2cm because they found no difference in metastasis-free survival or mortality in patients who were actively surveyed compared

with patients who underwent surgery for NF-pNETs <2cm (12). In addition to oncological safety, a non-interventional strategy for small NF-pNETs also mitigates against the high rate of major early post-operative complications, irrespective of tumour size, that has been reported for MEN1 patients undergoing pancreatic surgery (47) (**Figures 2D-E**). For example, an analysis of the early and late complications of surgical resection of NF-pNETs in a study of 63 patients with MEN1 found that: 33% of patients had major early surgical complications, most commonly due to severe pancreatic fistulas, which were associated with prolonged length of hospital attendance and significant readmission rates; 20% developed several major early complications; and 23% suffered from long-term complications (47). Collectively, these data highlight the risk of significant post-operative morbidity associated with pancreatic surgery in MEN1 (47).

The timing and extent of surgery in MEN1 is further complicated by the occurrence of multiple NF-pNETs in many patients and the formation of new tumours within the pancreatic remnant following previous surgery, rendering subsequent resections more challenging and probably further increasing the risk of complications (35) (**Figures 2F-G**). In these situations, surgical options are limited to aggressive approaches, including total pancreatectomy. Finally, it is noteworthy that in patients with MEN1, synchronous duodenal and pancreatic NETs may be present and should always be considered since their occurrence may influence the decision for surgical versus conservative management.

Given the significant morbidity associated with surgical resection of NF-pNETs in MEN1, there remains an unmet medical need for anti-proliferative medical therapies that may delay, or even prevent, the need for pancreatic surgery in MEN1 patients with single or multiple NF-pNETs. In this regard, somatostatin analogues (SSAs) have proven efficacy with respect to progression-free survival in non-MEN1 patients with advanced gastroenteropancreatic neuroendocrine tumours (48, 49). In the CLARINET study, which excluded patients with MEN1, lanreotide treatment reduced disease progression and prolonged progression free survival in patients with advanced metastatic pNETs (48). Despite inherent clinical and biological differences between non-MEN1 and MEN1 pNETs, and an absence of supportive clinical trial evidence, lanreotide is a recognised

treatment option for MEN1 patients with unresectable pNETs or advanced metastatic disease. However, given the frequency of post-operative complications associated with surgical resection of small NF-pNETs, it was postulated that somatostatin analogues may have potential as 'chemoprophylactic' agents against pNETs. Indeed, the somatostatin analogue pasireotide, was shown to have a chemopreventive action in the development of pNETs in a mouse model for MEN1 (50), thereby suggesting that somatostatin analogues may have a role in slowing the growth of early NF-pNETs (<2cm) and/or preventing the formation of new pNETs in MEN1 patients. Proof-of-concept evidence for this notion has been provided by one uncontrolled retrospective clinical study of 20 MEN1 patients with early pNETs (<2cm) (NF-pNETs (n=14), Zollinger-Ellison syndrome (n=5), and insulinoma (n=1)) who were treated with octreotide LAR (30mg intramuscularly every 28 days) over 12-75 months (51). In this study, the investigators found that octreotide LAR resulted in an objective tumour response in 10% of patients, stable disease in 80% of patients and disease progression in 10% of patients (51). However, it is notable that this study had several limitations, including the absence of a control arm, small sample size and retrospective design. Thus, a well-powered, prospective, placebo-controlled clinical trial is required to clearly establish whether SSAs may attenuate tumour growth and new tumour formation of early NF-pNETs in MEN1. However, such a clinical trial will be difficult to deliver given that the majority of MEN1 patients possess small and slow growing NF-pNETs and, in the absence of robust prognostic biomarkers associated with MEN1 NF-pNETs, identifying the patients most likely to derive benefit from this treatment will be challenging.

Conclusions:

NF-pNETs remain a major cause of premature mortality in patients with MEN1. Due to a limited understanding of tumour natural history and an absence of prognostic biomarkers, expert opinions are divided on their optimal clinical management. Although many questions regarding MEN1 associated NF-pNETs remain, since publication of the MEN1 clinical practice guidelines in 2012 a more refined understanding of tumour behaviour and the radiological techniques used for their detection has been established. This knowledge, coupled with emerging data relating to the morbidity associated with surgical resection of NF-pNETs in MEN1 and potential safety concerns associated with

surveillance strategies, suggests that it may be timely to revise the current follow up recommendations. However, a thorough systematic review of the currently available data is required to provide an evidence-based approach, and in its absence we advocate continuation of the guidelines recommended annual radiological surveillance with MRI for MEN1 patients. However, if surveillance yields a completely normal result, imaging every two-three years is likely to be sufficient. Currently available data suggest that screening for pNETs should commence between the ages of 10-16 years; however, further research is required to establish the optimal age to start pNET surveillance in MEN1 (13). Surgical resection is warranted for NF-pNETs >2cm, whereas conservative management is generally appropriate for tumours <2cm, accepting that a small proportion of patients may develop advanced disease. Given that NF-pNETs have distinct biological behaviours compared with non-MEN1 tumours, we discourage against the generalisation of findings from non-MEN1 clinical studies to the MEN1 population. Instead, we believe that it is vital that future MEN1 research focuses on the identification of prognostic biomarkers and surrogate clinical endpoints that will facilitate the delivery of innovative, multicentre prospective clinical trials that evaluate the effectiveness of anti-tumour therapies to guide the optimal management of NF-pNETs in MEN1.

Disclosures

BGC is an employee of AstraZeneca.

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Figure Legends

Figure 1.

(A) The European Neuroendocrine Tumour Society (ENETS) recommendations (2016) for the surgical management of NF-pNETs, which advocate surveillance rather than surgery for all incidentally discovered NF-pNETs <2cm (1). **(B)** The summary of the National Comprehensive Cancer Network (NCCN) guidance for NF-pNETs and recommends surgery for all NF-pNETs measuring >1cm (2). **(C)** The MEN1 clinical practice guidelines written by a self-assembled group of international experts, which suggests surgical resection for NF-pNETs >1cm (2).

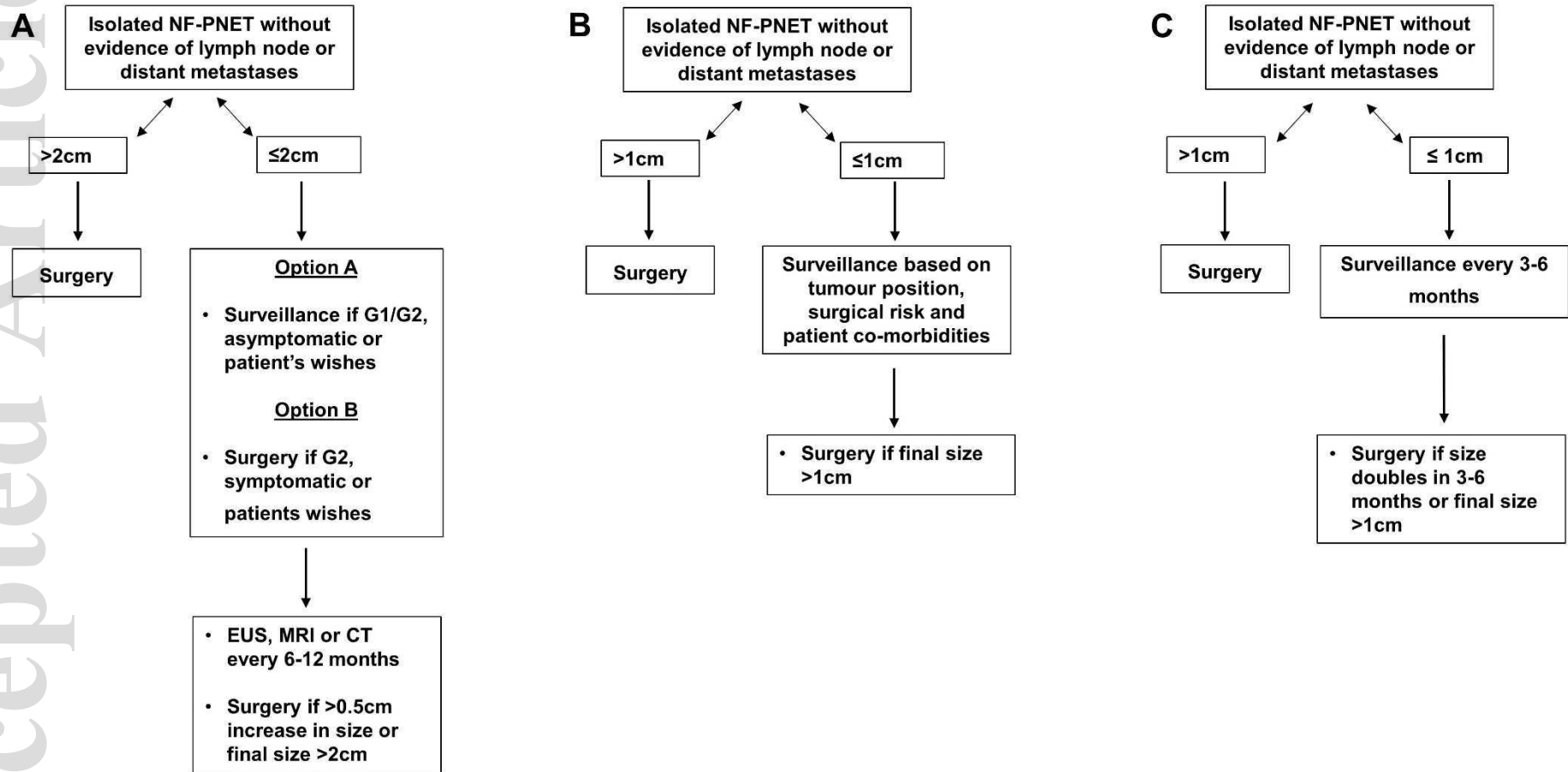
Figure 2.

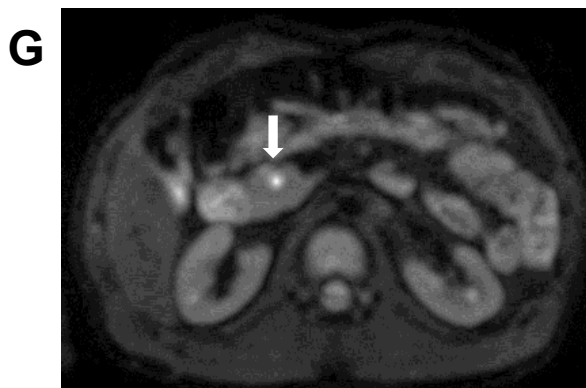
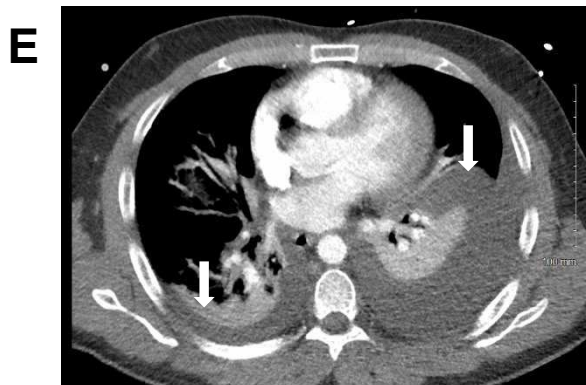
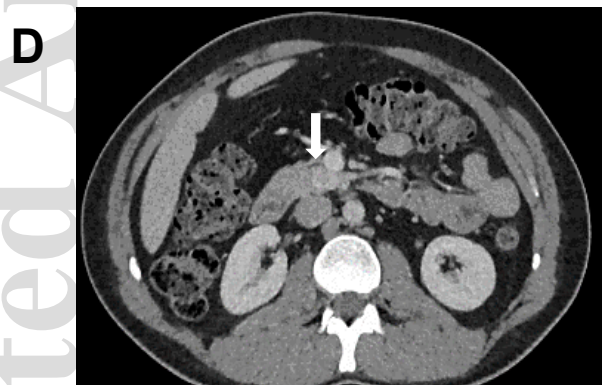
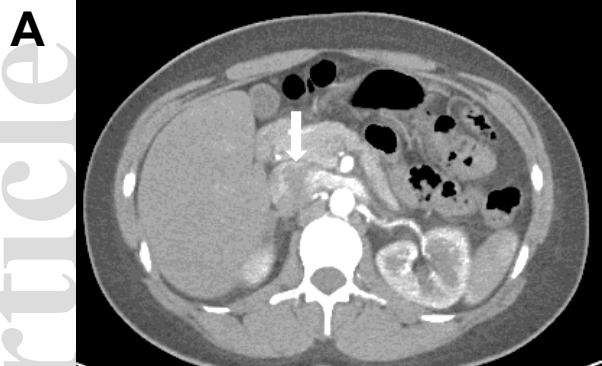
Case 1: Images **(A)** and **(B)** demonstrate a 2.8cm cystic NF-pNET in the pancreatic head visualised by CT imaging and EUS, respectively. The patient was referred for clinical surveillance at the age of 25 years following genetic confirmation of MEN1 identified through cascade family screening. **(C)** Low-avidity in the NF-pNET on ¹⁸F-FDG PET/CT imaging; following surgical resection and histological analysis, this correlated with a non-metastatic grade 2 well-differentiated pNET with 0/2 lymph nodes positive for metastatic disease.

Case 2: **(D)** An axial CT image demonstrating a 1.9cm NF-pNET in the uncinate process of the pancreas detected on the first surveillance scan in a 33-year old male with MEN1.

The patient underwent a Whipple's procedure at the patient's request. **(E)** An image from a post-operative CT pulmonary angiogram that illustrates left lower lobe collapse, consolidation in the right lung and bilateral pleural effusions (left>right) as demonstrated by the white arrows. The patient also developed severe remnant pancreatitis and necrosis, resulting in a prolonged hospital admission and significant long-term morbidity that impacted upon his livelihood and has severely compromised his quality of life.

Case 3: (F) Demonstrates a hyper-intense 1.5cm pNET in the pancreatic head visualised by MRI in a patient with MEN1. This patient had previously undergone a distal pancreatectomy for an insulin-secreting pNET and was subsequently diagnosed with the new 1.5cm NF-pNET in the remnant pancreas 4 years later. **(G)** Demonstrates that the lesion remained stable over a 4-year period of observation, and annual surveillance continues.





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Figure 2