**MEN1 SCREENING PROTOCOL**

Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant disorder due to mutations in the tumour suppressor gene MEN1, which predisposes to developing tumours. It is a hereditary syndrome most commonly characterized by parathyroid, enteropancreatic neuroendocrine, and anterior pituitary tumours. Other recognised features include thymic and bronchial carcinoid tumours, adrenocortical tumours, and cutaneous lesions.

Given the rarity of the disease (prevalence is estimated at 2-20 per 100,000 worldwide)1, the bulk of the literature on MEN1 is limited to observational studies with more prospective studies emerging with earlier diagnosis and genetic screening. As no phenotypic-genotypic correlation has been established, regular screening for tumours is necessary for all MEN1 patients and MEN1 mutation carriers. This protocol is based on published clinical practice guidelines and a literature review on MEN1-associated tumours.

List of abbreviations:

CgA : Chromogranin A

GHRH : Growth hormone-releasing hormone

GTE : Groupe d’étude des Tumeurs Endocrines

HPB : Hepatopancreatic biliary

MEN1 : Multiple endocrine neoplasia type 1

mTOR : mammalian target of rapamycin

NET : Neuroendocrine tumour

PHPT : Primary hyperparathyroidism

PP : Polypeptide

PTH : Parathyroid hormone

SRS: Somatastatin receptor scintigraphy

SUV: standard uptake value

TKR: Tyrosine kinase receptors

VIP : Vasoactive intestinal peptide

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 Tests and schedules to screen for endocrine tumours in MEN1 patients

|  |  |  |  |
| --- | --- | --- | --- |
| **Tumour****(estimated frequency)** | **Age to begin screening (yrs)** | **Annual biochemical tests** | **Imaging tests** |
| Parathyroid adenoma (90%) | 10 | Calcium (esp. iCa2+)PTH | Neck US and sestamibi, if calcium elevated and surgery is proposed |
| Gastrinoma (40%) | 10 | None, unless clinical suspicion or imaging identifies tumour(s) | 2 yearly MRI abdomen\* |
| Insulinoma (10-30%) | 10 | None, unless clinical suspicion or imaging identifies tumour(s) | 2 yearly MRI abdomen\* |
| Other enteropancreatic tumours(30- 70%) | 10 | None, unless clinical suspicion or imaging identifies tumour(s) | 2 yearly MRI abdomen\* |
| Anterior pituitary tumours(30-40%) | 10 | Prolactin, IGF1 | 2 yearly **non-contrast** MRI pituitary\* |
| Thymic and bronchial carcinoids(~3%) | 18 | None(typically non-secretory, but have malignant potential) | Low dose CT chest at age 18 or at time of diagnosis (if later) Low dose CT chest age 402 yearly MRI chest\* when CT chest not performed |
| Adrenal lesions (~20%) | 10 | None unless symptoms develop or identified tumour >1 cm58Renin, aldosterone, U&Es24hr UFC, overnight dexamethasone suppression test24hr urinary metanephrinesTotal testosterone, DHEA-S | 2 yearly MRI abdomen\* |

\* On TRAK book MRI chest/abdomen in same order as NON-CONTRAST MRI pituitary to ensure all scans are performed same day

1.0. Diagnosis

MEN1 diagnosis is based on one of three approaches, which are not mutually exclusive2:

1. Clinical: Presentation of 2 or more classic MEN1-related features primary hyperparathyroidism (PHPT), enteropancreatic neuroendocrine tumour, or pituitary tumour)
2. Familial: First degree relative (of an affected individual) expressing at least one clinical manifestation of MEN1
3. Genetic: MEN1 mutation carrier not manifesting any clinical disease

2.0. Primary hyperparathyroidism

This is the most common and usually the earliest endocrine expression of MEN1, occurring in 90% of MEN1 patients by the age of 40 years3. Features of primary hyperparathyroidism in MEN1 patients differ to non-MEN1 patients and include: earlier age at onset (25 years vs 55 years); equal male:female ratio (1:1 vs 1:3); and premature bone mineral density loss3-5.

Screening includes annual assessment of serum calcium and PTH concentrations3. Ionised calcium measurements can be a helpful addition as a more sensitive indicator of hyperparathyroidism especially in patients with intermittent or borderline elevation of total calcium6.

Neck ultrasound and sestamibi scans are the dominant imaging techniques used in the setting of primary hyperparathyroidism7. They can provide accurate preoperative localization with similar surgical success rates to traditional bilateral exploration7.

There are three goals for parathyroid surgery in MEN1 hyperparathyroidism: (i) to obtain and maintain normocalcaemia for as long as possible, (ii) to avoid permanent hypoparathyroidism, and (iii) to facilitate potential future surgery. Transcervical thymectomy is also recommended at time of surgery8. Clinical practice guidelines still advocate open exploration and subtotal parathyroidectomy (i.e. $\geq $ 3.5 glands) without imaging1 because of the inherently high relapse risk of a more limited resection9. However, four-gland parathyroid exploration carries a significant risk of hypocalcaemia when compared to less than three gland removal and similar conservative approaches10. Replacement therapy with vitamin D analogues can be problematic and result in increased urine calcium excretion, nephrocalcinosis, and impairment of general well-being11,12. Many of the patients with MEN1 undergoing parathyroid surgery are young and recurrence following a limited resection could occur many years later and dealt with by a further focused procedure10,13.

More recent retrospective studies have reported encouraging findings on minimally invasive parathyroidectomy when concordant preoperative localizing studies were performed. In a highly selected group of MEN1 patients there was 0% (0/6) and 13% (1/8) who developed persistence of disease after a mean follow-up of 19 and 47 months respectively10,13. There was no incidence of permanent hypoparathyroidism in either study. Other studies argue limited parathyroidectomy guided by preoperative localizing studies results in unacceptably high persistent and recurrent PHPT and suggest localization studies are not so accurate with enlarged contralateral parathyroid gland(s) frequently missed 14.

Controversy remains as to the appropriate timing of any parathyroid surgery. Early parathyroidectomy can reduce the exposure to long-term hyperparathyroidism as one study demonstrated that severe osteopenia affected 44% of MEN1 PHPT patients with mild, asymptomatic hypercalcaemia4. Another study demonstrated parathyroidectomy was associated with reduced fracture risk in all primary hyperparathyroidism cases with evidence of osteopenia or osteoporosis15. On the other hand, early surgery can also lead to an earlier recurrence of hyperparathyroidism or chronic treatment of hypoparathyroidism.

Discussion regarding management options (including a combination of localization studies, surgical referral, and active surveillance of biochemistry and end-organ complications) should be started when there is biochemical evidence of primary hyperparathyroidism. Patient’s should be actively involved in the decision making around the timing and nature of surgery.

2.1. We make the following recommendations for screening and treating primary hyperparathyroidism:

* Annual assessment of serum calcium and PTH. Ionised calcium should be checked if calcium is normal or intermittently high with a PTH higher than normal reference range
* Two consecutive adjusted calcium readings above normal range (> 2.60 mmol/l) should pre-empt focused consultation on the pros and cons of two management options:
	+ Imaging with surgical referral
	+ Continuing active surveillance with serum calcium, DEXA and imaging of the renal tract
* For those patients opting for surgery, pre-operative imaging should be requested and include neck ultrasound and sestamibi scan to locate any abnormally overactive or enlarged parathyroid gland(s)
* The surgical options include:
1. exploration and removal of all 4 parathyroid glands
2. 3.5 gland parathyroidectomy
3. removal of ipsilateral glands if a single abnormal gland is seen in imaging
* The pros and cons of each approach should be discussed with the patient
* Concurrent thymectomy should be considered at the time of parathyroid surgery, especially in men and those with a family history of thymic carcinoid (see subsection 5.2 on thymic carcinoid tumours)

3.0. Enteropancreatic neuroendocrine tumours

Incidence of enteropancreatic tumours varies from 30 to 80% in different studies2. The characteristics of MEN1 enteropancreatic tumours are heterogeneous as they can be single or multiple, benign or malignant, and they can be divided into hormonally active (functioning) tumours associated with a clinical syndrome (ie gastrinomas, insulinomas) or non-functioning tumours without any clinical manifestations (ie non-functioning pancreatic tumours). More than one enteropancreatic tumour type can also co-exist in MEN1.

In the past, significant mortality related to pancreatic tumours was due to late onset of diagnosis. Screening studies revealed that up to 50% of patients already had metastases by the time symptoms developed, particularly in functioning tumours such as gastrinomas16. Therefore, regular biochemical screening for pancreatic neuroendocrine tumours in MEN1 carriers was recommended to achieve early diagnosis and timely surgery for malignancy prevention2,3.

Current clinical guidelines for MEN1 call for annual screening with fasting plasma GI hormone profile including gastrin, insulin (with paired glucose), glucagon, vasoactive intestinal peptide (VIP), chromogranin A (CgA), and polypeptide (PP)3. Fasting plasma gastrin and insulin (with paired glucose) have high sensitivity for detecting development of gastrinomas and insulinomas respectively3,17. Such early screening can explain the decline in MEN1-related mortality in these tumours as seen in Table 118. Unfortunately, glucagon, CgA, and PP measurements for detecting non-functioning pancreatic tumours are less reliable with sensitivities of 43%, 33%, and 36% respectively19,20.

3.1. Non-functioning pancreatic tumours

Now, growing availability and sensitivity of radiological screening methods have resulted in increasing identification of non-functioning pancreatic tumours. Penetrance of all enteropancreatic tumours increases with age in MEN1 with one study reporting the age-specific penetrance to be 15% at age 30 years, 49% at age 50 years, and 68% at age 70 years21,22.

Early identification and surveillance of non-functioning pancreatic tumours remain clinically important as:

1. Recent studies indicate they are the most common enteropancreatic tumours in MEN1 and are associated with similar or worse prognosis than functioning tumours (i.e. gastrinoma and insulinoma respectively)23
2. Tumour size significantly correlates with metastases (4% if ≤ 1.0 cm, 10% if 1.1 to 2.0 cm, 18% if 2.1 to 3.0 cm, and 43% if > 3.0 cm; p<0.01)22
3. Malignant pancreatic NETs remain the commonest cause of mortality in MEN1 with 5 and 10 years survival being 75% and 50% respectively18,24

Current practice guidelines recommend annual radiological screening but cannot specify which imaging modality is best3,19. A combination of pancreatic and duodenal MRI, CT, and /or endoscopic ultrasound (EUS) are suggested.

Given the potential early age and frequency of imaging, MRI would be our recommended imaging modality to limit radiation exposure. MRI has similar sensitivity to CT imaging for enteropancreatic tumours as shown in table 6 . EUS has high sensitivity for detecting pancreatic tumours < 1 cm but it is also more invasive and has poorer sensitivity for detecting tumours on the left side of the pancreas25,26. Furthermore, detected tumours < 1 cm would not warrant surgery or medical treatment and only result in unnecessary anxiety. EUS would be more suitable for pre-operative localization of an already identified tumour rather than a screening tool.

Regular interval imaging will replace the need for annual fasting gut hormone profile and insulin measures for screening, though clearly these should be measured if a suspected neuroendocrine tumour is identified.

Factors suggested to be of prognostic value include World Health Organization (WHO) classification, proliferation indices (ie Ki-67), and tumour-node-metastasis (TNM) staging.

WHO classification divides tumours based on differentiation (table 3)27. Poorly differentiated neoplasms, which make up 10% of cases, have a definitive poor prognosis. The remaining 90% of pancreatic endocrine tumours are well-differentiated and yet their clinical behaviour can vary from indolent to highly malignant28.

Proliferation indices such as Ki-67 have been used to discriminate well-differentiated tumours. Tumours with a Ki-67 value greater than 2% have been associated with lymph node metastases and therefore favours surgery. However, this grading system has not been used in MEN1 tumours and requires further evaluation. Therefore, histology alone cannot predict clinical course.

TNM staging is commonly used in the assessment of tumours and potentially a useful prognostic indicator19,27,28. However, its use in pancreatic neuroendocrine tumours is relatively recent and two different classification systems exist - ENETs (European Neuroendocrine Tumor Society) and AJCC (American Joint Committee on Cancer)27. Its application in MEN1 should be considered with caution as most of these studies are focused in patients with non-familial (sporadic) pancreatic NETs and does not account for differences such as younger age of onset, multi-focality, and concomitant presence of other tumours seen in MEN1 patients27.

Management of enteropancreatic tumours is challenging when prognostic indicative tools have yet to be firmly established. The aim should be to reduce morbidity and mortality related to metastatic disease, while still preserving pancreatic tissue and avoiding surgical complications.

From the established literature, recommendations to date have been based on tumour size with the observation that there is an increase rate of metastases in patients with larger tumours22. The largest reported cohort study (n=108) demonstrated low mortality risk and development of lymph nodes and/or metastasis in MEN1 patients with < 2 cm non-functioning pancreatic tumours (3% who underwent surgery died of the disease, 7.7% had synchronous lymph nodes or distant metastases, 19% had distant metastasis based on imaging) after a 4 year follow-up 29,30. Other case series have reported similar findings of distant metastases (6 to 22%)29. Long-term follow-up data is still needed. The majority of centres advocate surgery if the tumour measures > 2 cm or is rapidly growing22.

Surgery should be aimed at excising every tumour while preserving the spleen and as much pancreatic tissue as possible19,22. Specific surgical management is out with the remit of this protocol. However, it will certainly require a multidisciplinary approach with HPB surgical input.

Medical therapy is a potential consideration in unresectable tumours or advanced metastatic disease. Several treatments for sporadic pancreatic neuroendocrine tumours have been studied and are discussed in more detail.

Somatostatin analogues (ie octreotide and lanreotide) have been used in non-MEN1 patients with treatment-naïve, well-differented enteropancreatic tumours with significantly increased median progression-free survival31,32. One retrospective study of octreotide LAR treatment included 20 MEN1 patients with pancreatic tumours > 2 cm which showed objective tumour response in 10%, stable disease in 80%, and disease progression in 10% over 12-75 months of therapy33.

Cytotoxic chemotherapy has also been used in non-MEN1 pancreatic tumours with large tumour burden and/or progressive metastatic disease. Streptozocin and 5-fluorouracil (5-FU) and/or doxorubicin demonstrated objective tumour response of 36-40% with median progression free-survival of 13-18 months34. Temozolomide with capecitabine also showed objective tumour response of 70% with median progression free-survival of 18 months35. These chemotherapy regimens have not been evaluated in MEN1 patients.

Inhibitors of tyrosine kinase receptors (TKR) like sunitinib have been reported to be effective in treating pancreatic NET. Treatment with sunitinib in advanced, well-differentiated pancreatic NET led to increased overall survival and doubling in progression-free survival when compared to patients receiving placebo (11.5 vs 5.5 months, p < 0.001)36.

Everolimus, an oral inhibitor of mammalian target of rapamycin (mTOR), has also shown anti-tumour activity in patients with advanced pancreatic neuroendocrine tumours. Everolimus given to advanced low-grade or intermediate-grade pancreatic neuroendocrine tumours demonstrated a doubling of median progression-free survival when compared to patients receiving placebo (11.0% vs 4.6, p < 0.001)37. These studies on TKR and mTOR inhibitors are based largely on sporadic cases of pancreatic NETs. However, there is reasonable assumption they would be just as effective in MEN1 related pancreatic NETs.

Other specific advanced disease therapy include radiofrequency ablation, hepatic artery embolization (HACE), and peptide radio-receptor therapy**3**. Indications for these treatment(s) would take a multidisciplinary approach and more likely to be an adjunct or third line agent to other treatment options described above.

3.2. Functioning pancreatic neuroendocrine tumours

3.2.1. Gastrinomas

Gastrinomas are the most common functional MEN1-associated enteropancreatic tumours. Approximately 40% of MEN1 patients develop gastrinomas before the age of 402. Patients with established disease often present with recurrent or multiple peptic ulceration marked with hypergastrinaemia, a condition referred to as Zollinger-Ellison syndrome (ZES)38. Symptoms preceding diagnosis include abdominal pain, dyspepsia, and diarrhoea (table 4).

ZES often co-exists with primary hyperparathyroidism and consequently hypercalcaemia is frequently seen with hypergastrinaemia. Management of primary hyperparathyroidism to restore normal calcium levels can help improve clinical symptoms and gastrin levels in up to 20% of MEN1 patients39.

The majority of gastrinomas in MEN1 patients are located within the duodenum, are multiple and small (< 0.5 cm)3,16,19. Although less frequent, these tumours can also occur in the pancreas. It is important to remember that in a patient with ZES, an observable tumour in the pancreas cannot be presumed to be the gastrinoma, as non-functioning tumours can co-exist and the gastrinoma(s) are often microscopic.

Previous mortality from GI haemorrhage has significantly reduced since the introduction of drugs inhibiting gastric-acid secretion. Now, the major cause of mortality is due to malignant sequelae related to tumour site, tumour size, and presence of hepatic metastases3,40. Aggressive disease, defined as an increase in tumour growth $\geq $ 25% per month or new lesion(s) at annual follow-up, has been shown to significantly decrease survival41. Otherwise, survival in MEN1 patients with gastrinomas < 3 cm is relatively good and has been reported to be 95% at 15 years and 52% at 15 years if hepatic metastases are present (lymph node metastases does not adversely affect survival)3. At present, there are no clinical or molecular genetic factors that can distinguish an aggressive phenotype. Therefore, confirming diagnosis and regular imaging is key.

Diagnosis is made with fasting gastrin measures ten times the upper limit of normal (i.e. gastrin > 100 pg/ml) in the presence of hyperchloryhydria or pH $\leq $2. To exclude other potential diagnoses (*Helicobacter pylori* infection, antral G-cell hyperplasia, gastric outlet obstruction), a provocation test is sometimes used with calcium infusion (4 mg Ca2+/kg/hr for 3 hours)3.

Current guidelines advocate medical therapy for hypergastrinaemia with histamine-2 receptor antagonist and proton pump inhibitor (PPI). Long-term, frequent and high doses of PPIs to maintain subphysiologic gastrin levels have not been shown to be harmful in patients with ZES42,43.

The role of surgery remains contentious. Surgery is not always warranted as biochemical cure rate is poor and clinical studies suggest there is no difference in long-term survival between medically and surgically treated MEN1 patients44,45. The 2016 ENETs guidelines would not recommend routine surgical exploration in MEN1/ZES patients with tumours $\leq $ 2 cm and would only suggest surgery in patients with enteropancreatic tumours > 2 cm46.

A history of abdominal pain, dyspepsia, and diarrhoea should be obtained at annual review and fasting gastrin measured if there is clinical suspicion47. MRI abdomen every 2 years is recommended for surveillance. We advocate an MDT approach to discuss treatment options for tumour(s) > 2 cm on imaging and for poorly controlled ZES despite medical therapy.

3.2.2. Insulinomas

These occur in 10-30% of MEN1 cases and are often solitary and intrapancreatic. However, they can also be associated with other pancreatic neuroendocrine tumours at time of diagnosis in 19% of patients in MEN148. Age of onset is younger then 40 years, which differs from non-MEN1 patients who present over the age of 403. Surgical removal is recommended because risk of severe hypoglycaemia and unknown effect of long term medical management. Among the different forms of pancreatic neuroendocrine tumour, insulinomas have a better prognosis as seen in table 218.

A history of possible hypoglycaemia should be obtained at annual review and home blood glucose monitoring and/or prolonged fasting performed if there is clinical suspicion. MRI abdomen is recommended for active surveillance. However, if there is a high index of clinical suspicion, CT and EUS are additional imaging modalities for pre-operative localisation of the insulinoma.

**3.2.3 Other functioning pancreatic neuroendocrine tumours (table 4)**

Glucagon-secreting pancreatic tumours occur in fewer than 3% of patients with MEN1. 50 to 80% of patients have metastases at time of diagnosis.3 A history of diarrhoea, skin rash (necrolytic migratory erythema), weight loss, symptoms of hyperglycaemia, and stomatitis should be elicited at annual review.

VIPomas have been reported in only a few MEN1 patients.3 A history of watery diarrhoea and hypokalaemia should be obtained at annual review.

GHRHomas are also reported in some patients with MEN1. Approximately 33% of these patients will have other MEN1-related tumours. More than 50% arise in the lung, 30% in the pancreas, and 10% in the small intestine2,3.

Somatistatinomas are associated with hyperglycaemia, cholelithiasis, diarrhoea, and steatorrhoea. 7% of MEN1 enteropancreatic tumours are reported to secrete somatostatin but they do not always correlate with symptoms3. Paradoxically, hormonal symptoms from somatostatinomas may respond to somatostain analogue therapy.

3.3. We make the following recommendations for screening enteropancreatic neuroendocrine tumours:

* Annual review for clinical manifestations of functional tumours
* Abdominal MRI every 2 years
* If imaging identifies pancreatic tumour(s), fasting gastrin, insulin (with paired glucose), and gut hormone profile should be performed
* If imaging identifies pancreatic tumour(s) > 2 cm or rapidly growing tumour(s) from serial imaging then referral to the HPB and neuroendocrine MDT should be made to consider surgery, medical therapy, or other targeted therapies in the case of advanced disease

4.0. Pituitary tumours

Incidence of pituitary tumours in MEN1 patients vary from 15 to 50% in different series. Approximately 60% of MEN-1 associated pituitary tumours secrete prolactin, 25% secrete growth hormone, and the remainder appear to be non-functioning. There is a wide range to age of onset with a reported mean age ± SD of 38 ± 15.3 years2,3.

MRI imaging is recommended in practice guidelines3. A finer point is whether contrast is necessary. More recent studies have suggested gadolinium is retained in intracranial neuronal tissues irrespective of renal or hepatobiliary dysfunction49. While long-term clinical significance is unclear, it is prudent to avoid overexposure to contrast-enhanced MRI50,51. We advocate a non-contrast study given the lifetime frequency of scans.

4.1. We make the following recommendations for screening pituitary tumours:

* Annual surveillance of prolactin and IGF-1
* Non-contrast MRI pituitary every 2 years

5.0. Intrathoracic Carcinoid tumours

5.1. Bronchial carcinoid tumours

Bronchial carcinoid tumours occur in 3.4 to 13.3% of MEN1 patients18,52. In reported studies, the majority of these patients are diagnosed by regular radiological screening. Gender differences are inconsistent in the literature. Tumour size can be < 10 mm at diagnosis, and some pulmonary nodules thought to be bronchial carcinoid have been later determined to be metastases from other neuroendocrine tumours. One study reported rate of tumour growth to be 17% per year and this was independent of baseline tumour size52. This highlights the importance of imaging and recognizing that small pulmonary nodules in this cohort are more likely to grow compared to small pulmonary nodules seen in normal population.

When, if any, surgical intervention is required for bronchial carcinoids is unclear. Studies suggest bronchial tumours are not associated with increase mortality in comparison to pancreatic and thymic neuroendocrine tumours (table 2). Survival did not appear to differ between operated and non-operated patients. In current guidelines, surgery is still advised for lung neuroendocrine tumours and can facilitate pathology to help determine further course of action3. Further evaluation is still required to determine tumour behaviour between sporadic and MEN1-related atypical carcinoids, where the former is recognized to have a poor prognosis and 5 year survival of 44-78%53.

5.2. Thymic carcinoid tumours

Prevalence of thymic neuroendocrine tumours in MEN1 ranges from 2% to 8.2% in different studies, again with the higher prevalence reported in single-centre, prospective studies with patients actively screened for these tumours1,54. From collected studies in Europe, thymic tumours predominantly occur in men (male/female ratio, 20:1); an exception to this is a Japanese series where 36% of the patients were women55,56. While no genotypic-phenotypic correlation has been established for any MEN1 tumour, several studies report familial clusters with thymic tumours which would certainly suggest a heritable genetic component.57 Cigarette smokers also appear to have a higher risk in developing these tumours3.

In the French and Belgian GTE cohort of 761 MEN1 subjects, the youngest patient identified with a thymic tumour was age 16 who died 49 months after diagnosis from metastases. With this exception, thymic tumours developed after the age of 21, with a mean age at time of diagnosis 42.7 years. Within this group 85.7% (18/21) had hyperparathyroidism and 40% (6/15) of these patients had parathyroidectomy with preventative thymectomy. Despite surgery, there was recurrence in 33% (2/6); this can be explained by the approach taken as cervical thymectomy may still leave an intrathoracic part of the thymus behind1. Therefore surgical referral and assessment for thymectomy should be made based on indication (see subsection 5.3 on recommendations).

Thymic carcinoids are associated with a significantly high mortality risk (hazard ratio 4.64, 95% CI 1.73 – 12.41). Median survival after diagnosis of a thymic tumour has been reported to be approximately 9.5 years with a 10-year probability survival of 36.1% (range, 11.5 – 62%)1,18. The poorer prognosis may be related to advanced disease found at presentation as most patients do not have classical features of carcinoid syndrome.

Generally, carcinoid tumours in MEN1 can be asymptomatic and may not display clinical features until a late stage expressing malignancy. Given the aggressive nature of thymic tumours that can potentially occur at any age, early identification is necessary. However, no hormonal or biochemical abnormality is consistently observed in individuals with these carcinoid tumours. Therefore, screening is highly dependent on radiological imaging and survival rate may be improved with regular imaging.

In regards to imaging, CT scans were performed in several studies and has a reported sensitivity of 95% (21/22) for detecting thymic carcinoid1,54. There is clearly a concern about using CT as a screening modality in patients with a tumour diathesis, particularly at young age. Chest CT is though generally superior to chest MRI in detecting intra-thoracic lesions. MRI has only been used in one study but with an overall sensitivity of 100% (7/7).

5.3. We make the following recommendations for screening bronchial and thymic tumours:

* Low dose contrast CT chest for clear visualization of thymus and chest be performed at two milestone ages with interim MRI chest every 2 years
* Given the aggressive nature of thymic carcinoids and the potential early age of onset we suggest that the earliest age low dose CT chest is performed is at age 18 or at diagnosis (if at a later age).
* Another low dose constrast CT chest should be performed age 40
* Interim MRI chest should be performed every 2 years
* Concurrent thymectomy should be considered at the time of parathyroid surgery, especially in men. Thymectomy should also be considered in kindreds with a history of thymic carcinoid. Transcervical thymectomy is unlikely to remove all thymic tissue and so a detailed discussion with the endocrine surgical team is required to plan the optimal surgical approach. This is likely to include a combined transcervical thymectomy and a video-assisted mediastinoscopic thymectomy in high risk patients.
* Identification of any carcinoid tumour should be discussed at the NET MDT

6.0. Adrenal tumours

In the prospective GTE cohort study (n =715 MEN1), adrenal enlargement was reported in 20.4% (146/715) and adrenal tumours ( i.e. > 10 mm in size) reported in 10% (72/715). Patients seldom presented with clinical symptoms alone (11%) and the majority (75%) were diagnosed on routine screening58.

Most adrenal lesions (i.e. cortical adenomas, hyperplasia, multiple adenomas, nodular hyperplasia, cysts, or carcinoma) are non-functioning. Less than 10% of patients exhibit endocrine hypersecretion, and among these primary hyperaldosteronism and ACTH-independent Cushing’s syndrome are the most commonly seen. Hyperandrogenaemia and phaeochromocytoma can occur but are uncommon. Adrenal hypersecretion was isolated to MEN1 patients with tumours > 1 cm in size in the GTE cohort. Therefore detailed hormonal evaluation would be advocated in patients with tumours > 1 cm in size or in the presence of clinical features (subsection 6.1) 58.

The GTE study highlighted the significantly higher prevalence of adrenal cortical carcinoma (ACC) in MEN1 patients with adrenal tumours compared to normal population with adrenal incidentalomas (13.8 vs 1.3%, p < 0.05)58.

Several observed characteristics of MEN1 ACCs (n = 10) include58:

1. 50% were small in size ( < 50 mm) at diagnosis
2. 90% displayed ENSAT stage I or II which would allow for complete surgical resection59
3. 20% had more than one tumour and 10% had bilateral tumours
4. 20% developed during follow-up of relatively small adrenal nodules, some of which were < 10 mm in size

These observations potentially reflect the impact active surveillance has on early surgical management, although longer-term clinical outcomes have yet to be established.

6.1. We make the following recommendations for screening adrenal tumours:

* 2 yearly MRI abdomen
* If adrenal adenoma identified and > 1 cm in size then endocrine investigations should be performed to investigate following conditions:
	+ Primary hyperaldosteronism: renin, aldosterone, renal function
	+ ACTH-independent Cushing’s syndrome: 24hr urinary free cortisol, overnight dexamethasone suppression test
	+ Phaeochromocytoma: 24hr urinary metanephrines
	+ Androgen-secreting tumour: plasma total testosterone, DHEA-S
* Decision regarding surgical referral should be made with reference to the ECED protocol on “Investigation and follow-up of the incidental adrenal mass”.

7.0. Cutaneous manifestations

Subcutaneous lipomas are frequently multiple and occur in more than 33% of patients with MEN1. Management is conservative.

Multiple facial angiofibromas and collagenomas occur more frequently in MEN1 patients and may provide a useful diagnostic tool to identifying MEN1 in patients with already known enteropancreatic tumours17. Treatment for these lesions is not required.

# **8.0 Genetics**

In clinical practice genetic mutational analysis for MEN1 has several important purposes60:

1. Confirmation of diagnosis
2. Identification of positive kindreds to facilitate early, regular screening
3. Identification of 50% of family members who do not have the germline mutation to allay any anxiety over future tumour burden for them and their progeny

MEN1 mutation testing should be offered to3 :

1. Any patient with two or more MEN1-associated tumours
2. Any patient with clinical suspicion of MEN1 syndrome (i.e. multiple parathyroid adenomas age < 45 years61; recurrent hyperparathyroidism, multiple enteropancreatic neuroendocrine tumours at any age)
3. First-degree relatives of a known MEN1 mutation carrier regardless of symptoms

*Age-related disease penetrance is near zero below age 5 years, over 50% by 20 years, and above 95% by 40 years62. It is our recommendation genetic screening be offered starting at age 10, thjough some centres advocate screening at the age of 5 years..*

5 to 10% of patients with clinical MEN1 may not have an identifiable mutation in the MEN1 gene3. An alternative genetic diagnosis should be sought according to clinical suspicion (table 5)60. Potential alternative genetic causes include: CDKN1B, CDKN1A (p21), CDKN2B (p15), CDKN2C (p18), HRPT2/CDC73, CASR, and AIP.

When screening family members in a confirmed MEN1 kindred, the possibility of phenocopy should also be considered. Phenocopy refers to the development of disease manifestations associated with mutations of a particular gene (i.e. phenotype) but which are due to another aetiology3. For example, a family member in a kindred presents with hyperparathyroidism; the familial Menin mutation is not identified in this family member and it transpires that they have sporadic hyperparathyroidism.

Confirmed MEN1 cases should be referred to Clinical Genetics for construction of pedigree and identification of at risk/affected family members. If the mutation found in the proband cannot be detected in either parent, this can still be explained by a germline mosaicism in a parent or a *de novo* mutation in the proband64. Therefore, genetic screening to other first degree relatives is still warranted in these cases. As tumour penetrance and malignancy cannot be predicted individually, lifelong screening of MEN1 carriers is necessary to prevent tumour morbidity.

Prenatal testing for MEN1 is not commonly requested and there is a lack of consensus on performing such a diagnosis in MEN164. Preconception advice should be based on establishing linkage in the family with the involvement of Clinical Genetics to discuss the genetic risk of MEN1 inheritance and relevant screening process for children.

9.0 Functional Imaging

Gold standard functional imaging for neuroendocrine tumours (NETs) is somatostatin receptor scintigraphy (SRS), which targets somatostatin receptor type 2 (SSTR2)47. However, diagnostic sensitivity is variable ranging from 65-100% depending on origin of tumour, density and type of SSTRs expressed on tumour cell surface, and tumour size.

Now PET/CT with somatostatin receptor tracers 68Gallium-DOTA-TATE, 68Gallium-DOTATOC, or 68Gallium-DOTA-NOC has been proven to be as clinically effective for evaluating neuroendocrine tumours. These tracers have high affinity for SSTR2 but also bind to other SSTR subtypes which can be clinically relevant in some tumour types. An overall sensitivity and specificity of 91.7% and 93.5% respectively have been reported for detecting neuroendocrine tumours in MEN syndromes65. Another study suggested enteropancreatic tumours had a significant risk to disease progression with an SUVmax > 12.3 based on ROC analysis (area under the curve 0.97; SE = 0.045; p = 0.016)66.

Presently, ENETs has recommended the use of 68Gallium-labeled somtatostatin receptor PET/CT for diagnostic purposes in patients with non-familial, rare functional NETs46. It is useful for staging and also for detecting early recurrences after resection of NET(s), which we believe would be similarly advantageous in MEN1 management.

One recent prospective study on 7 MEN1 subjects reported 68Ga-DOTATATE PET/CT was superior to other functional and anatomic imaging in the detection of primary and metastatic enteropancreatic tumours. Based on positive findings, patient management was changed in 31% (8/26) patients because of the risk of primary malignant tumour or detection of metastatic tumour initially not identified. However, false positives are a potential issue and influenced surgical management in a few cases67. Some of this may be due to indeterminate uptake (SUVmax < 10) although some false positive lymph nodes had high SUVmax at 21 and 34.

 68Ga-DOTATATE PET/CT is a consideration for MEN1-associated tumour sites with malignant potential such as enteropancreatic neuroendocrine and intrathoracic carcinoid tumours. Given the novelty of this diagnostic modality, there is little evidence-base as to whether this affects long-term patient outcomes but certainly reports are favourable towards its application in tumour staging67.

**Table 1: Causes of death in GTE cohort with diagnosis before 1990 collected retrospectively and after 1990 collected prospectively with regular genetic and tumour screening18**

|  |  |  |
| --- | --- | --- |
|  | Diagnosis before 1990 | Diagnosis after 1990 |
| Related to MEN1 | 53 (76.8%) | 25 (71.4%) |
| Due to ulcerous disease (perforation or haemorrhage) | 10 (14.5%) | 1 (2.8%) |
| Due to local or metastatic progression | 33 (47.8%) | 23 (65.7%) |
| Zollinger-Ellison | 12 | 6 |
| Insulinoma | 3 | 0 |
| Glucagonoma-vipoma-somatostatinoma | 2 | 2 |
| Nonfunctioning pancreatic tumour | 5 | 6 |
| Thymic tumour | 2 | 3 |
| Bronchial tumour | 5 | 0 |
| Gastric tumour | 0 | 1 |
| Pituitary tumour | 1 | 1 |
| Adrenal tumour | 2 | 1 |
| Brain tumour | 1 | 1 |
| Unknown primary tumour | 0 | 2 |
| Other reasons related to | 10 (14.5%) | 1 (2.8%) |
| Zollinger-Ellison | 2 postoperative deaths | 1 acute pancreatitis |
|  | 1 chemotherapy |  |
|  | 1 septicaemia |  |
| Insulinoma | 1 postoperative death | 0 |
|  | 1 hypoglycaemia-related suicide |  |
| Glucagonoma-vipoma-somatostatinoma | 1 postoperative death | 0 |
| Hyperparathyroidism | 2 acute hypercalcaemias | 0 |
| Pituitary tumour | 1 postoperative death | 0 |
| Unrelated to MEN1 | 13 (18.8%) | 10 (28.6%) |
| Other cancers | 8 | 3 |
| Other medical causes | 5 | 7 |
| Unknown causes | 3 (4.4%) | 0 (0%) |

**Table 2: Mortality risk dependent on MEN1-associated tumour4**

**Risk of death according to MEN1 lesion (GTE cohort) using a frailty model**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Hazard ratio | 95% CI | p |
| Women vs men | 0.46 | 0.28-0.76 | 0.003 |
| Familial history of MEN1 | 0.46 | 0.27-0.79 | 0.005 |
| Period of diagnosis |  |  |  |
| 1980-1989 vs <1980 | 0.33 | 0.18-0.60 | <0.001 |
| 1990-1995 vs <1980 | 0.18 | 0.09-0.35 | <0.001 |
| ≥1996 vs <1990 | 0.17 | 0.08-0.40 | <0.001 |
| Neuroendocrine thymic tumour | 4.64 | 1.73-12.41 | 0.002 |
| GVS | 4.29 | 1.54-11.93 | 0.005 |
| Nonfunctioning pancreatic tumour | 3.43 | 1.71-6.88 | 0.001 |
| Gastrinoma | 1.89 | 1.09-3.25 | 0.022 |
| Adrenal tumour | 1.72 | 0.97-3.06 | 0.064 |
| Bronchial tumour | 1.55 | 0.64-3.77 | 0.332 |
| Pituitary tumour | 1.17 | 0.72-1.90 | 0.536 |
| Insulinoma | 0.85 | 0.39-1.86 | 0.679 |

GVS glucagonoma or vipoma or somatastastinoma

**Table 3**

**Tumour grading: WHO 2010**

Figure 1ψ 

|  |
| --- |
| **Histopathology of Neuroendocrine Tumors68** |
| **Histological Classification** | **Well Differentiated** **(Low Grade, G1)** | **Moderately Differentiated (Intermediate Grade, G2)** | **Poorly Differentiated (High Grade, G3)** |
| Appearance | Monomorphic population of small, round cells | \* | Cellular pleomorphism |
| Prognosis | Prolonged survival | Intermediate | Poor |
| Mitotic Rate | <2 | 2–20 | >20 |
| Ki-67 Index+ | <3% | 3–20% | >20% |
| Necrosis | Absent | \* | Present |

\*Not well defined in medical literature

+ Ki-67 index applies only to WHO and European Neuroendocrine Tumor Society (ENETS) classification of gastroenteropancreatic NET

ψ Images courtesy of Nasir Aejaz, MD, Department of Pathology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

**Table 4: Functional enteropancreatic tumour syndromes**47

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Name | Biologically active peptide(s) secreted | Incidence per million per year | % MEN1 | Main symptoms/signs |
| Insulinoma | Insulin | 1-3 | 4-5 | * hypoglycaemic symptoms (100%)
 |
| ZES | Gastrin | 0.5-2 | 20-25 | * pain (79-100%)
* diarrhea

(30-75%)* oesophageal

symptoms(31-56%) |
| VIPoma | VIP | 0.05-0.2 | 6 | * diarrhea

(90-100%)* hypokalameia (80-100%)
* dehydration (83%)
 |
| Glucagonoma | Glucagon | 0.01-0.1 | 1-20 | * rash (67-90%)
* glucose intolerance

(38-87%)* weight loss (66-96%)
 |
| GRHoma | GHRH | Unknown | 16 | * acromegaly (100%)
 |
| Somtatostatinomas | Somatatostatin | Rare | 45 | * diabetes (63-90%)
* cholelithiases

(65-90%)* diarrhea (35-90%)
 |

VIP vasoactive intestine peptide; GHRH growth hormone releasing hormone

**Table 5: Familial syndromes17**

|  |  |  |  |
| --- | --- | --- | --- |
| **Disorder** | **Tumours (estimated penetrance)** | **Gene** | **Chromosomal location** |
| MEN1 | Parathyroid adenoma (90%)Enteropancreatic tumour (30-70%)- Gastrinoma (40%)- Insulinoma (10%)- Non-functioning & PPoma (20-55%)- Glucagonaoma (<1%)- VIPoma (<1%)Pituitary adenoma (30-40%)- Prolactinoma (20%)- Somatotrophinoma (10%)- Coticotrophinoma (< 5%)- Non-functioning (< 5%)Other associated tumours- Adrenal cortical tumour (40%)- Phaeochromocytoma (< 1%)- Bronchopulmonary NET (2%)- Thymic NET (2%)- Lipomas (30%)- Angiofibromas (85%)- Collagenomas (70%) | MEN1 | 11q13.1 |
| MEN2A | Medullary thyroid cancer (90%)Phaeochromocytoma (50%)Parathyroid adenoma (20-30%) | RET | 10q11.21 |
| MEN2B/MEN3 | Medullary thyroid cancer (90%)Phaemochromocytoma (40-50%)Associated abdnormalities (40-50%)- Mucosal neuromas- Marfanoid habitus- Medullated corneal nerve fibres- Megacolon | RET | 10q11.21 |

|  |  |  |  |
| --- | --- | --- | --- |
| MEN4 | Parathyroid adenomaPituitary adenomaReproductive organ tumours- Testicular cancer- Neuroendocrine cervical carcinomaAdrenal and renal tumours | CDKN1B | 12p13.1 |
| HPT-JT | Parathyroid adenoma (90%)Parathyroid cancer (15%)Ossifying fibromas (30%)- mandible-maxillaKidney lesions (10%)- bilateral cysts- renal harmatomas- Wilms tumours | HRPT2/CDC73 | 1q31.2 |
| FHH1FHH2FHH3 | No tumours, hypercalcaemia (100%) | CASRGNA11AP2S1 | 3q13.3-q21.119p13.319q13.32 |
| FIHP 69 | Parathyroid adenoma | Incomplete expression from MEN1, HRPT2, CASR, CDKN1A (p21), CDKN2B (p15), CDKN2C (p18) | 11q13, 1q31.2, 3q21.1, 6p21.2, 9p21, 1p32 |
| FIPA | Pituitary adenoma (ACTH-secreting, growth hormone-secreting, prolactin-secreting) | AIP | 11q13.2 |

FHH familial hypocalciuric hypercalcaemia; HPT-JT hyperparathyroidism-jaw tumour syndrome; FIHP familial isolated hyperparathyroidism; FIPA familial isolated pituitary adenomas

**Table 6: Sensitivity of different imaging modalities for neuroendocrine tumours and pulmonary nodules**

|  |  |  |  |
| --- | --- | --- | --- |
| **Tumour type** | **Imaging Modality** |  | **Sensitivity** |
| Enteropancreatic tumours |  |  |  |  |
| Sporadic | EUS (n = 39)70 |  |  | 82% |
|  | EUS (n = 32)71 |  |  | 94%  |
|  | EUS + CT with thin sections (n = 18) 71 |  |  | 100% |
|  | CT with thin sections (n = 18)71 | 94% |
|   | MRI (n = 20)72 |  |  | 85%  |
| MEN1 | EUS (n = 28)73 |  |  | 82% |
|  | EUS (n =35)19 |  |  | 100% |
|  | CT (n = 43)19 |  |  | 81% |
|  | MRI (n = 8)19 |  |  | 88% |
|  | SRS (n = 32)19 |  |  | 84% |
| Thymic carcinoid tumours |  |  |  |  |
| MEN1 | CT (n = 6)54 |  |  | 100% |
|  | CT (n = 9)1 |  |  | 100% |
|  | MRI (n = 6)54 |  |  | 100% |
|  | SRS (n = 4)54 |  |  | 75% |
|  | SRS (n = 2)1 |  |  | 100% |
| Sporadic pulmonary nodules |  |  |  |  |
|  | MRI (T2-HASTE)74 |  |  |  |
|  |  > 10 mm |  |  | 100% |
|  |  6 – 10 mm |  |  | 95.7% |
|  |  3 – 5 mm |  |  | 86.3% |
|  |  < 3 mm |  |  | 73% |
|  | Low dose CT75 |  |  |  |
|  |  < 4mm |  |  | < 1% |
|  |  ≥ 4 mm |  |  | 97.6% |

CT, computed tomography; MRI, magnetic resonance imaging; EUS, Endoscopic ultrasound; AUSS, abdominal ultraouns scan; SRS, Somatostatin receptor scintigraphy Number in parentheses indicate number of patients investigated.

**Table 7: Comparison of radiation doses from medical imaging tests and background radiation76**

|  |  |  |
| --- | --- | --- |
| Examination | Radiation dose (mSv) | Time to accumulate comparable natural background dose |
| CT |  |  |
| **Low dose Chest** | **1.5** | **6 months** |
| **Chest** | **7** | **2 years** |
| Chest (PE) | 10 | 3 years |
| Abdomen and pelvis | 10 | 3 years |
| **Multiphase abdomen and pelvis** | **31** | **10 years** |
| Radiography |  |  |
| Chest | 0.1 | 10 days |
| Lumbar Spine | 0.7 | 3 months |
| Abdomen | 1.2 | 5 months |
| Other |  |  |
| Mammography | 0.7 | 3 months |
| DEXA | 0.001 | <1 day |

 mSv millisievert, a measure of ionizing radiation on the human body

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