The future: surgical advances in MEN1 therapeutic approaches and management strategies

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Abstract

Multiple endocrine neoplasia type 1 (MEN1) is a hereditary autosomal dominant disorder associated with numerous neuroendocrine tumors (NETs). Recent advances in the management of MEN1 have led to a decrease in mortality due to excess hormones; however, they have also led to an increase in mortality from malignancy, particularly NETs. The main challenges are to localize these tumors, to select those that need therapy because of the risk of aggressive behavior and to select the appropriate therapy associated with minimal morbidity. This must be applied to a hereditary disease with a high risk of recurrence. The overall aim of management in MEN1 is to ensure that the patient remains disease- and symptom-free for as long as possible and maintains a good quality of life. Herein, we review the changes that occurred in the last 20 years in the surgical management of MEN1-associated functional and non-functional pancreatico-duodenal NETs and thymic and bronchial NETs.

Introduction

The management of MEN1-associated NETs has evolved over the last 20 years. A major advance in the management of patients with MEN1 is the possibility to control most of the excess production of different hormones, leading to a major decrease in mortality caused by hormone excess; this was the cause of death for more than 75% of the patients in some early series (Ballard et al. 1964, Lamers 1978, Majewski & Wilson 1979, Vasen et al. 1989). This decrease in mortality from hormone excess led to an increase in mortality from malignancy, particularly from neuroendocrine tumors (NETs) (Goudet et al. 2010, Ito et al. 2013). Researchers recognized early the aggressive potential of different NETs (for example, pancreatico-duodenal NETs, mainly non-functional (NF), and thymic NETs); however, they also recognized the deleterious effects of aggressive surgery, leading to numerous modifications in the recommendations over the last two decades.

Despite the rarity of MEN1, many high-quality studies have been performed recently. In this review, we will describe the main changes that have occurred in the last 20 years in the surgical management of MEN1-associated NETs.

Duodeno-pancreatic NETs

Duodeno-pancreatic NETs (pNETs) in MEN1 are either functional or NF and secrete many different hormones,
such as gastrin, insulin, pancreatic polypeptide (PP) or vaso-intestinal polypeptide (VIP), which are associated with distinct clinical syndromes. The incidence of pNETs in patients with MEN1 varies between 30 and 80% (Brandi et al. 2001, Goudet et al. 2011). Usually pNETs have an earlier onset in patients with MEN1 than in those without (Triponez et al. 2006a, Machens et al. 2007) and their hallmark is multiplicity in contrast to solitary sporadic pNETs. The main challenge is to locate the functional tumor among the NF tumors.

**Gastrinoma and Zollinger–Ellison syndrome**

The management of patients with Zollinger–Ellison Syndrome (ZES) and MEN1 (ZES/MEN1) is more specific than that of patients with other types of pNETs related to MEN1, especially NF tumors. ZES/MEN1 is a fairly common condition, as 20–30% of patients with ZES have MEN1 (Mignon & Cadiot 1998, Falconi et al. 2016). ZES is the most frequent functioning pNET type in patients with MEN1, with an incidence of up to 28.5% in the ‘Groupe d'études des tumeurs neuro-endocrines’ (GTE)-MEN1 cohort of a total of 758 patients (Goudet et al. 2010). Its prevalence has proportionally decreased over time because of the easier recognition of NF-pNETs resulting from improvement in imaging techniques, notably endoscopic ultrasound (EUS) and magnetic resonance imaging (MRI) (Triponez et al. 2006a).

Pathologically, almost all gastrinomas are found in the duodenal wall (Anlauf et al. 2007, Falconi et al. 2016) and are associated with hyperplastic gastrin cell lesions and very small gastrin-producing micro-tumors of less than 0.5 mm in diameter. Furthermore, multiple pancreatic NETs are almost always associated with duodenal NETs. They less commonly produce gastrin and cause ZES (<15%) (Anlauf et al. 2007, Falconi et al. 2016), as most are NF tumors. However, they can secrete glucagon and/or pancreatic polypeptide (Anlauf et al. 2007). These tumors are usually small; in a French series of 77 patients with ZES–MEN1, only 10 had pNETs measuring 3 cm or more (Cadiot et al. 1999).

Prognostically, specific survival is mainly determined by liver metastases (Goudet et al. 2010, Ito et al. 2013). Gastrinomas have a higher mortality rate than insulinomas, but not than other types of pNETs, notably NF-pNETs (Goudet et al. 2010). In the 2 largest series of patients with ZES–MEN1, the prevalence of liver metastases was 6–16% at the time of diagnosis (Jensen et al. 2008) and their risk of developing liver metastases was 9–10% at 8–9 years (Cadiot et al. 1999). The only predictive factor for developing liver metastases is the size of pNETs, with a 2.5–3 cm threshold in older series (Cadiot et al. 1999, Norton et al. 2001) and a 2 cm threshold in the more recent studies. However, it is unclear whether the metastases came from the gastrinomas or the NF-pNETs. This threshold is currently used for the management of patients with MEN1 and NF-pNETs (Partelli et al. 2016, Triponez et al. 2006b, 2017). In patients with non-metastatic disease and ZES–MEN1, 6% of those without a large pNET (<3 cm) developed liver metastases compared with 40% of those with pNET ≥3 cm, although the resection of the largest tumors was performed in 9 out of 10 patients with large tumors (Cadiot et al. 1999). The long-term prognosis of patients without large pNET or liver metastases is very good, reaching 95% at 10 years (Gibril et al. 2001). In patients with ZES/MEN1 who had an unfavorable outcome, 14% had aggressive tumor growth, more metastases (liver 100% vs 10% in patients with a favorable outcome, bone 38% vs 0%) and a shorter survival (88% vs 100% during follow-up) (Gibril et al. 2001). Clinically, the main question is how to identify patients at high risk of metastases or death when they do not have large tumors. The role of histo-prognostic factors such as tumor grading obtained by EUS-guided biopsy has not been studied in MEN1 patients. Fluorodeoxyglucose positron emission tomography (FDG-PET) positivity is associated with higher grade pNETs in patients with MEN1 (Kornaczewski Jackson et al. 2017). Studies are required to determine whether this could be used to select patients with ZES–MEN1 at risk of metastases or death.

Questions about the management of patients with ZES and MEN1 concern ZES diagnosis, the search for tumors, treatment of the consequences of gastric hypersecretion and the treatment of these tumors.

**Diagnosis of ZES**

Gastrin-immunoreactive NETs, i.e. gastrinomas, must be distinguished from NETs associated with a functioning syndrome, i.e. ZES; this is determined by gastric acid hypersecretion because of unregulated tumor-related hypergastrinemia. Compared with sporadic NETs, in MEN1, we can observe the early development of functioning syndromes such as ZES, because patients with MEN1 are young. Patients with ZES and MEN1 are on average 10 years younger than those with sporadic ZES at the time of diagnosis (Jensen et al. 2008, Singh et al. 2012). Therefore, ZES should be considered in patients...
with MEN1 with new digestive symptoms, including loose stools, especially when diarrhea promptly disappears when using proton pump inhibitor (PPI) therapy, epigastric pain and signs of gastroesophageal reflux even without severe esophagitis or tiny duodenal erosions on gastroscopy. Even so, since ZES is relatively frequent in MEN1, when hypergastrinemia occurs in patients with MEN1 without typical or pathognomonic signs of ZES, other causes must be considered, especially for PPI therapy and pernicious anemia. Diagnosis of ZES relies on both basal gastric acid outputs and serum gastrin measurements, sometimes with secretin or more rarely calcium stimulation (Mignon & Cadiot 1998, Ito et al. 2012). Biological criteria for the diagnosis of ZES are the same in patients with or without MEN1 (Mignon & Cadiot 1998). One major drawback is the necessity of measuring gastric acid secretion, as currently few departments are able to perform it (Ito et al. 2012, Falconi et al. 2016). Finally, hyperparathyroidism-related hypercalcemia can increase gastric acid output, and it is therefore usually recommended to treat hyperparathyroidism before the pNETs.

Tumor localization

Compared with other pNETs linked to MEN1, the peculiarities of ZES are the localization of gastrinomas in the duodenal wall and their multiplicity. Furthermore, they are usually small and difficult to find. The tumor workup must also include a search for metastases. For duodenal gastrinomas, investigation includes gastroscopy and EUS; however, their sensitivity is probably low and they have not been specifically studied in the setting of ZES/MEN1. The gold standard modalities for pancreatic gland analysis in patients with MEN1 are EUS and MRI, which are complementary (Barbe et al. 2012). Although the sensitivity of EUS is much higher than that of MRI for the detection of pNETs (Thomas-Marques et al. 2006, Barbe et al. 2012, Kappelle et al. 2017), larger tumors (>2 cm) can be found using MRI, especially in the pancreatic tail (Barbe et al. 2012). Liver MRI is the reference imaging modality for the detection of liver metastases (d’Assignies et al. 2013). Gallium-68 DOTATOC PET/CT may become the technique of choice in the future; however, this has not yet been evaluated correctly (Froeling et al. 2012).

Peculiarities of ZES treatment in patients with MEN1

Compared with NF-pNETs, the treatment of the ZES includes the control of gastric acid hypersecretion and, surgically, the treatment of multiple duodenal tumors that secrete gastrin.

Anti-secretory treatment

There is no difference in anti-secretory treatment depending on whether the ZES is sporadic or not (Mignon & Cadiot 1998). When ZES is suspected, PPI therapy must be administered promptly because complications from peptic lesions can develop rapidly (Ito et al. 2012). If possible, serum gastrin should be drawn and gastric juice pH should be determined before beginning PPI (Ito et al. 2012). Modalities of PPI therapy have not changed recently.

Anti-tumor therapy

Management of the tumors relies on the specific individualized therapeutic aims. Theoretically, the main goal is to reduce mortality and the second goal is to cure ZES. However, this can only be achieved if all gastrinomas are resected, which necessitates aggressive resection (Whipple procedure or partial pancreatectoduodenectomy) (Mignon & Cadiot 1998, Norton et al. 2001, Jensen et al. 2008, Imamura et al. 2011, Lopez et al. 2013). Some groups perform duodenectomy without pancreatectomy, associated with lymph node resection (Imamura et al. 2011). Such aggressive surgery allowed long-term eugastrinemia in 92% of patients compared with 33% in a short series with a median follow-up of 136 months (Lopez et al. 2013). In a series from the NIH, studying non-aggressive surgery, a ZES cure was never obtained; however, the survival rates were high at 100% and 86% at 5 and 10 years, respectively (Norton et al. 1999). The Whipple procedure and partial pancreatectoduodenectomy significantly reduces the risk of recurrence of ZES and the risk related to re-operation, but is probably associated with higher mortality and morbidity than less extensive resection. Aggressive surgery in MEN1 patients often showed low mortality rates and non-different morbidity rates compared with less aggressive surgery (Lopez et al. 2013), although the same results were not reported in every series (You et al. 2007). However, these were small studies involving experts in the field, which does not reflect real clinical scenarios.

Rendering patients eugastrinemic is different to curing ZES, which is based on negative secretin tests in the long term; the former has not been evaluated in terms of tumor recurrence in the pancreas, metastasis development and survival. About 20–30% of patients with ZES/MEN1 have fundic carcinoids, usually multiple, and some of these have malignant potential (Lehy et al. 1992, Berna et al. 2008). Some patients undergo total gastrectomy for that.
reason (Lehy et al. 1992, Berna et al. 2008) and we can suppose that fundic carcinoid development is probably reduced when eugastrinemia is obtained.

Based on other pNETs data, we can anticipate that tumor resection reduces metastases development. However, this has not been proven in patients with MEN1, regardless of whether ZES was present. Even in sporadic ZES, the demonstration of a reduction in liver metastases development relies on very few data obtained in non-comparative studies (Fraker et al. 1994). In patients with ZES/MEN1, surgery was not associated with a decrease in metastases (Cadiot et al. 1999, Jensen et al. 2008, Singh et al. 2012). This could be: 1- because the risk of metastases is late and low, requiring a very long follow-up to be able to show differences in the risk; 2- because patients underwent surgery too late to reduce metastases development. Indeed, for most experts, surgery is confined to patients with large tumors (>2–2.5 cm) or to those with growing tumors and 3- because the type of surgery is not appropriate.

In practice, considering the mortality and morbidity rates of aggressive surgery of the duodenum and pancreas, the long-term functioning sequelae (including diabetes, pancreatic insufficiency, dumping and bloating), the risk of recurrence related to MEN1 and the low risk of metastases in the long term for small tumors (<2 cm), whether they be gastrinomas or NF tumors, we and most experts recommend limiting surgery to patients with large tumors (>2 cm) and to those with a growing tumor. Surveillance should be performed in other situations (Fig. 1). We define significant growth as a 25% increase in >1 cm tumors (Triponez & Cadiot 2007).

The surgical approach that is most widely used is enucleation (EN) for tumors of the pancreatic head with duodenotomy and resection of the duodenal tumors, lymph node resection and, in some cases, distal pancreatectomy (Jensen et al. 2008, Thompson 1998a). The Whipple procedure or partial pancreaticoduodenectomy is indicated when tumors of the duodenum or pancreatic head are large and not enucleable. Other pancreatic tumors are therefore enucleated. Median pancreatectomy can be performed for centrally located lesions that are unsuitable for surgery. Finally, total duodeno-pancreatectomy is very rarely performed because of the high risk of sequelae, notably life-threatening diabetes.

For other groups, systematic surgery is indicated as soon as pNETs are demonstrated regardless of their size (Bartsch et al. 2005, Tonelli et al. 2006, Lopez et al. 2013). Surgery type can be determined by the source of hypergastrinemia, shown using a selective arterial secretin injection angiography (SASI) test. A Whipple procedure for other groups, systematic surgery is indicated as soon as pNETs are demonstrated regardless of their size (Bartsch et al. 2005, Tonelli et al. 2006, Lopez et al. 2013). Surgery type can be determined by the source of hypergastrinemia, shown using a selective arterial secretin injection angiography (SASI) test. A Whipple procedure

\[ \text{Figure 1} \]
Management of MEN1 patients with ZES.

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1 some teams may perform SASI test
2 almost all gastrinomas in MEN1 patients are small duodenal tumours and the identified pancreatic tumours on imaging studies are often NF-pNETs (see also Fig. 3)
3 some teams favour a more aggressive surgery for ZES
4 follow-up imaging similar than for NF-pNETs (see Fig. 3)
5 some teams favour a duodenotomy + excision of duodenal tumours while other teams favour a complete excision of the duodenum (Whipple, partial pancreaticoduodenectomy or pancreas-preserving total duodenectomy) for the management of ZES
is performed when it is localized to the duodenum/pancreatic head (Imamura et al. 2011, Lopez et al. 2013).

The endpoint used to compare both types of management (i.e. systemic intervention vs selective intervention and also the Whipple procedure vs limited surgery) should be overall survival. In a previous study, there was a tendency for better survival in the ‘aggressive’ group, but this was not significant (overall 10-year survival rates were 100% for the ‘active’ group (n=13) and 78% for the other group (n=9) (P=0.155) (Lopez et al. 2013). Disease-specific mortality at 10 years was 100% in the first group vs 89% in the other group (P=0.409) (Lopez et al. 2013).

These different ways of treating patients have not been compared prospectively and they are the subject of much debate.

**Type of surveillance**

Whether patients have undergone surgery or not, surveillance of the duodeno-pancreas and the main metastatic sites is mandatory. MRI with diffusion sequences is the most sensitive conventional imaging technique for the detection of liver metastases of NETs (d’Assignies et al. 2013). Theoretically, this should be performed annually.

Concerning the pancreas, we propose to perform both MRI and EUS and then to choose one of the techniques according to its ability to detect and measure tumors. These recommendations are applicable for NF-pNETs and ZES in the context of MEN1. However, a direct comparison of both techniques to detect a significant increase in the size of the tumors has not been conducted. The rate of increase in size has been shown to be low with MEN1 tumors that secrete VIP are rare. Patients develop necrolytic migratory erythema, weight loss, stomatitis and anemia, although all of these may be absent. The gold standard for the diagnosis of insulinoma is a 48-h supervised fast with negative levels of beta-hydroxybutyrate and sulfonylurea with a threshold for proinsulin of ≥22 pmol/L (Guettier et al. 2013). Because of their small size (82% <2 cm, 47% <1 cm), insulinomas are difficult to localize and are scattered throughout the pancreas gland (Service et al. 1991). Ultrasound (US), CT and MRI are widely used for detection, with EUS showing positive results in up to 95% of cases (McLean & Fairclough 2005). If these studies are negative, more invasive techniques, such as selective angiography with intra-arterial calcium stimulation and hepatic venous sampling for insulin levels, localize >80% of insulinomas (Brown et al. 1997, Guettier et al. 2009). Additionally, new somatostatin receptor (SSTR)-targeting PET modalities, such as 68Gallium-DOTATATE, are adjunct modalities for localization (Sadowski et al. 2015, 2016, Nockel et al. 2017). As insulinomas express glucagon-like peptide 1 (GLP1) receptor more than SSTR, PET imaging with labeled GLP1 analogs might be a promising tool (Antwi et al. 2015).

Intraoperative US (IOUS) with bimanual palpation improves the success rate of surgery, and blind distal pancreatic resections should be avoided (Hirshberg et al. 2002, Nikfarjam et al. 2008).

Functional glucagonomas occur in <3% of patients with MEN1 and their clinical manifestations are skin rash (necrolytic migratory erythema), weight loss, stomatitis and anemia, although all of these may be absent. The most frequent location is in the tail of the pancreas and glucagonomas are often metastatic at the time of diagnosis. MEN1 tumors that secrete VIP are rare. Patients develop watery diarrhea, hypokalemia and achlorhydria. The diagnosis is established when elevated plasma VIP levels are associated with an excess stool volume of 0.5–1 L per day during fasting. VIPomas are also frequently located in the pancreatic tail.

The management aim is to ensure that these patients remain disease- and symptom-free for as long as possible and maintain a good quality of life. The main goal for patients with symptomatic functioning pNETs is to cure the functioning syndrome. This is obtained using surgery with careful evaluation of the extent of the disease prior to planning specific therapy (Thakker et al. 2012). Contrary to the recommendations for surgical resection in NF-pNETs based on tumor size (Sadowski & Triponez 2015), the timing and extent of resection for functional pNETs are still debated, especially regarding the type of resection for multiple tumors in patients with MEN1. With MEN1 developed insulinoma (Goudet et al. 2015). The gold standard for the diagnosis of insulinoma is the timing and extent of resection for functional pNETs.
(Jensen & Norton 2017). Furthermore, unlike ZES/MEN1, which requires Whipple resections for cure, functional pNETs are generally curable without extensive resections; however, they may recur (Falconi et al. 2016).

It is generally accepted that surgical intervention should be performed in patients with MEN1 who have hypoglycemia/hyperinsulinism (Jensen et al. 2012). In patients with MEN1, hyperinsulinism may be caused by one insulinoma surrounded by multiple other functioning or NF-pNETs (Mignon et al. 1993); thus, the surgical approach is debated. The risk of recurrence persists over the patient’s lifetime because of germline mutations. Experts concur that total pancreaticoduodenectomy (PD) as an initial procedure should only be used under exceptional circumstances given the long natural course of this disease. Furthermore, PD results in severe insulin-dependent diabetes mellitus and exocrine pancreatic insufficiency, with significant morbidity and reduction in quality of life for these generally young patients. Many authors have thus proposed distal pancreatic resection (DPR) associated with EN of any additional tumors in the pancreatic head as the treatment of choice for hypoglycemic symptoms (Cougard et al. 2000, Hellman et al. 2000, Giudici et al. 2012). Furthermore, EN is an attractive parenchyma-sparing strategy, especially for single dominant pNETs (Lopez et al. 2011, Bartsch et al. 2013). Some centers have reported a pancreatic fistula rate after EN of 24%, with no recurrences at the site of EN on long-term follow-up (median 77 months) (Nikfarjam et al. 2008); however, other studies have reported rates of recurrence of up to 57% after EN. Nikfarjam and coworkers advocate a re-operation policy for patients with MEN1 and recurrent insulinoma as an alternative to subtotal pancreatectomy (Nikfarjam et al. 2008). Moreover, additional pancreatic surgery in high-volume centers has a low morbidity (Norton et al. 2003). An important point in favor of limited resection is the guarantee of cure of hyperinsulinism with intraoperative confirmation of complete resection of the hypersecreting tumor tissue. This can be achieved using rapid intraoperative insulin immuno-chemoluminescent assays, measured before and after resection with results obtained within a short period of time and confirming completeness of resection, with or without concomitant glucose measurements (Proye et al. 1998, Carneiro et al. 2002, Jensen et al. 2012). However, there are little data in patients with MEN1, and because basal insulin level can be normal or released into the blood by surgical maneuvers, a recent study in MEN1 recommends to determine insulin levels during pancreatic manipulation in order to have a good basal reference and evaluate the insulin/glucose ratio (Giudici et al. 2012).

A large retrospective French multicenter study of 73 patients with MEN1-insulinoma revealed that DPR was associated with the highest symptom-free survival and manageable morbidity (Fig. 2) (Vezzosi et al. 2015). No recurrences were reported after DPR combined with EN for additional tumors in the pancreatic head. However, there were more complications after DPR than after EN procedures (short-term 30.4 vs 22.2%) and more long-term complications, such as endocrine and exocrine insufficiency. Diabetes occurred in 90% of patients who underwent DPR and in none of the patients who underwent EN alone. The overall cure rate was 82.2% and reached 91.3% with DPR after median follow-up of 9 years. Thus, DPR is associated with a low risk of hypoglycemic symptom recurrence, but because of the low morbidity, EN alone might be considered an alternative in patients with MEN1 (Vezzosi et al. 2015). In EN, an open or laparoscopic approach did not significantly alter the risk of recurrence of hypoglycemia symptoms.

Another recent study (Tonelli et al. 2017) compared 8 DPRs and 4 PDs in 12 patients with MEN1 with a clinical diagnosis of insulinoma. Forty percent of patients had multiple insulinoma, which was associated with additional NF-pNETs in all patients, and 4/12 patients (33%) had...
metastatic lymph nodes. Overall, 9 patients underwent additional EN during their surgery. The decision between the 2 types of resection was based on the distribution of tumors within the pancreas. The study concluded that, if the head of the pancreas is the most affected site and ZES is concomitant, PD is preferable over DPR.

Minimally invasive surgery is advancing and allows the use of accurate pre- and intraoperative localization modalities. These are mandatory to help localize a tumor during surgery and avoid making a simple procedure more extensive (Whipple/PD). There have been few studies in patients with pNETs and MEN1. Laparoscopic IOUS has transformed the approach to pNETs. In particular, in laparoscopic surgery, in which there is no tactile sensation for the surgeon, IOUS has gained results similar to open surgery. The lack of tactile sensation has been cited as an important factor in the failure to identify lesions and the resulting conversion to open surgery (Iliara et al. 2001, Aggeli et al. 2016). Laparoscopic pancreatic surgery started 20 years ago and has evolved to be safe in high-volume centers with results comparable with those of open PD (Correa-Gallego et al. 2014). Although mostly performed for solitary lesions, in patients with MEN1, minimally invasive procedures can be performed with similar safety to that of open procedures. Furthermore, minimally invasive procedures are associated with a shorter hospital stay and similar rates of postoperative complications (e.g. fistula) (Lopez et al. 2016).

Management of malignant insulinoma requires special attention. This is a rare condition that occurs in about 4–14% of cases and is defined as local recurrence, local invasion into surrounding tissues or the presence of lymph node or distant metastases. Tumors of grade 2 or higher according to the World Health Organization 2010 classification and those with peri-neural or lympho-vascular invasion are also included. General management goals for malignant functioning pNETs are symptom control and tumor volume reduction, with surgery recommended if the lesions are resectable (Pavel et al. 2012, Baudin et al. 2014). To further control symptoms or in non-surgical unresectable situations, adjuvant treatment is available, ranging from diazoxide and somatostatin analogs to everolimus and chemotherapy, local therapies (RFA, chemo-embolization, or radiotherapy) or peptide radio-receptor therapy (PRRT).

In conclusion, there is currently no consensus available about the extent of resection in functional pNETs for patients with MEN1 and future studies are needed. Pre- and peri-operative evaluation of number, size and localization of functional pNETs and associated syndromes (e.g. ZES) are important factors to determine the extent and type of surgical resection and increase the chance of a cure. Future knowledge about the mutational landscape of pNETs will allow a more personalized approach (Scarpa et al. 2017).

Non-functional pancreatic NETs

The standardization of biochemical and imaging protocols for the follow-up of patients with MEN1 has led to a large increase in the detection of NF tumors of the pancreas in these patients (Thomas-Marques et al. 2006, Thakker et al. 2012, Pieterman et al. 2014). Moreover, histopathological analysis of resected MEN1-pancreases has shown numerous micro-tumors that were not identified using imaging studies (Anlauf et al. 2006), further emphasizing the diffuse involvement of the pancreas in patients with MEN1. Historically, NF tumors were diagnosed late because of local symptoms and were associated with a high lethality early in life (Wilkinson et al. 1993, Doherty et al. 1998, Goudet et al. 2010, Ito et al. 2013). Indeed, the mean age of death for patients who died because of NF-pNET was 43 in a previous registry-based study (comprising patients diagnosed with MEN1 in France from 1956 to 2003) and 46 in the study by Doherty and coworkers analyzing patients registered in the Washington University database (Doherty et al. 1998). The high prevalence and lethality of pancreatic tumors led some authors recommending an aggressive management of those tumors. The ‘Norman Thompson procedure’ was popularized in the 1980s. This approach includes left pancreatectomy and enucleation of tumors in the head of the pancreas (since 1978) and duodenotomy with lymph node dissection in patients with concomitant ZES (duodenotomy was introduced systematically in patients with ZES in 1986). Thompson was convinced about the superiority of this aggressive management over more conservative approaches (Thompson 1998a,b) and convinced other surgeons to use similar approaches (in particular Akerstrøm in Uppsala, Sweden and Praye in Lille, France) (Skogseid et al. 1996, Bartsch et al. 2000, Dean et al. 2000, Akerstrom et al. 2002, Dralle et al. 2004, Proye 1998). At that time, a correlation between primary tumor size and the presence of metastases had already been described (Akerstrom et al. 1991), but the proponents of aggressive management believed strongly that ‘earlier detection and excision of tumors favors the possibility of a curative rather than palliative procedure’ (Thompson 1998a). Very good
long-term results with low surgical morbidity were reported (Thompson 1998a,b). In fact, he describes ‘no operative morbidity’ but he did not give details about operative morbidity. These internationally recognized surgeons were so convinced about this aggressive management that they carefully followed their patients and re-operated on them as soon as new tumors were evidenced biochemically or morphologically.

Despite repeated surgeries performed by internationally recognized experts, there were some disease-specific deaths and significant peri-operative mortality and morbidity. The Ann Arbor group carefully analyzed their patients and reported a median of 2 additional surgeries among 49 patients with MEN1, including 8 who needed completion pancreatectomy and duodenectomy (leading to total PD) after a median follow-up of 12 years. There were 7 complications related to surgery, including 1 death after enterocutaneous fistula and 3 patients who required insulin pumps to treat postoperative diabetes. Despite the aggressive protocol, 2 patients died of metastatic pNETs (Hausman et al. 2004, Gauger et al. 2009). Nell and coworkers (Nell et al. 2016) also reported 33% of major early complications and 23% of endocrine and/or exocrine insufficiency among 61 patients with MEN1 who underwent pancreatic surgery in a Dutch academic center. These patients were young (median 41 years old) and in good general health (ASA score I or II for 89% of the patients), further emphasizing the negative impact of complications in this population.

After re-operating on a significant number of patients with MEN1 and experiencing the deleterious effects of this aggressive approach, different teams tried to evaluate the risk-benefit ratio of extensive/repeated pancreatic procedures for these tumors. By analyzing the French registry data, we confirmed the correlation between tumor size and the risk of metastasis (Triponez et al. 2006a) and the low risk of disease-specific death in patients with NF-pNET ≤2 cm (Triponez et al. 2006b). Furthermore, these favorable results were confirmed after a mean follow-up time of 10.7 years; out of 46 patients with NF-pNETs ≤ 2 cm, only 1 patient died of the disease; 16 showed significant disease progression (indicated by an increase in the size or number of tumors, development of a hypersecretion syndrome or need for surgery); however, these patients could be treated accordingly with none presenting with metastasis at the end of the follow-up (Triponez et al. 2017).

Almost simultaneously, the DutchMEN1 Study Group analyzed data from 152 patients with MEN1 and NF-pNET. They reported that surgery for small NF-pNETs ≤2 cm was not associated with a significantly lower risk of liver metastases or death and concluded that the majority of patients with MEN1 and NF-pNETs ≤2 cm could be safely managed by watchful waiting, thereby avoiding major surgery without increasing the risk of metastasis or death (Nell et al. 2017). The effect of surgery for tumors 2–3 cm was uncertain and the authors suggested an international randomized study to evaluate the effect of surgery on patients with MEN1 and NF-pNETs of 2–3 cm. In their population, changing the surgical strategy from performing surgery for patients with NF-pNETs of 1 cm to performing surgery for patients with NF-pNETs of 2 cm would lead to a reduction of 59% in the number of pancreatic procedures.

The least invasive procedure is usually considered the best option. Lymph node dissection should be added to pancreatic resection and adapted to the type (in particular ZES vs NF-pNET) and location of the tumors (Falconi et al. 2016).

There are currently several different recommendations for the management of patients with MEN1 and small NF-pNETs. The Clinical Practice Guidelines for MEN1 (Thakker et al. 2012) suggest surgical resection for NF-pNETs >1 cm in size; similar guidelines are proposed by the Uppsala group (Akerstrom et al. 2012), the Marburg group (Bartsch et al. 2005) and the MEN consortium in Japan (Hanazaki et al. 2013). The National Comprehensive Cancer Center in the USA suggests a more conservative approach for tumors of 1–2 cm (www.nccn.org, version 3.2017). The European Neuroendocrine Tumor Society (Falconi et al. 2016) and the GTE (Triponez et al. 2006b) also suggest conservative management of NF-pNETs <2 cm if there are no signs of aggressiveness, such as rapid progression, on imaging studies. We believe that 2 very recently published studies (Nell et al. 2017, Triponez et al. 2017) will lead to a more uniformly accepted recommendation to use a watchful waiting strategy for NF-pNETs of ≤2 cm (Fig. 3).

**Thymic NETs**

**Introduction**

Thymic tumors are rare. They are the most frequent etiology of anterior mediastinal tumors. Histological classification subdivides these tumors into thymoma (subtypes A, AB, B1, B2, B3), thymic carcinoma (primarily squamous cell carcinoma) and more rarely
NETs. Thymic neuroendocrine tumors (TNETs) account for 2–5% of all thymic tumors. TNETs are classified as well-differentiated (typical and atypical) carcinoids or poorly differentiated (large-cell neuroendocrine and small-cell) carcinomas (Marx et al. 2015). Most TNETs are sporadic, but some are associated with MEN1 (TNETs-MEN1). This association was described for the first time in 1972 by Rosai and coworkers based on three case reports (Rosai et al. 1972). TNETs-MEN1 are characterized by genotype-phenotype correlations with MEN1 mutations, strong heritability and a poor outcome with frequent recurrences and a higher risk of death (Goudet et al. 2009, Thevenon et al. 2015, de Laat et al. 2016).

Incidence

The incidence of TNETs-MEN1 varies from 2 to 8%. Goudet and coworkers reported 21 TNETs among 761 patients with MEN1 (2.8%) from the GTE series (Goudet et al. 2009). In Dutch, North American and Italian series, the incidence of TNETs-MEN1 was 3.4, 2 and 3%, respectively (Ferolla et al. 2005, de Laat et al. 2014, Singh Ospina et al. 2015). In a prospective study of 85 patients with MEN1, Gibril and coworkers identified 7 TNETs (8%) (Gibril et al. 2003).

Diagnosis and screening

Once a diagnosis of MEN1 is established, explorations for a thymic tumor are required. Radiological screening should start at the age of 15 years and should be repeated every 1–3 years (Thakker et al. 2012). To limit radiation exposure, thoracic low-dose CT scan or MRI is recommended. There is no biochemical test for screening and/or diagnosis of TNETs-MEN1. Screening is required regardless of gender and smoking status, since publications did not confirm that TNETs-MEN1 occurred exclusively in males and smokers (Christakis et al. 2016). At diagnosis, most patients with TNETs-MEN1 are asymptomatic, without carcinoid syndrome; however, liver, bone and lung metastasis (synchronous or metachronous) may be found.

Prognosis

In a Japanese study of 1320 patients with thymic tumors (1093 thymomas, 186 thymic carcinomas, 40 sporadic TNETs and 1 TNETs-MEN1), the 10-year survival rate for thymic carcinoids was 80%, while it was 90% for thymomas and 50% for thymic carcinomas (Kondo & Monden 2003). In contrast, TNETs-MEN1 has a high mortality rate. In the GTE series, the median survival was...
9 years and 7 months, and the 10-year survival rate was 36% (Goudet et al. 2009). Patients with MEN1 had an increased risk of death when they had TNETs (HR = 4.64); however, this was not the case if they had bronchial NETs (br-NETs) (Goudet et al. 2010). In cohorts with MEN1 from Utrecht ($n=323$) and MD Anderson ($n=291$), the 10-year survival rates for the 11 and 9 cases of TNETs-MEN1 were 25% and 45%, respectively (Fig. 4A,B) (de Laat et al. 2014, Christakis et al. 2016), confirming the increased aggressiveness of these tumors in patients with MEN1 compared with sporadic tumors.

**Treatment**

Multidisciplinary management of thymic tumors is recommended. In France, the RENATEN (endocrine tumors) and RYTHMIC (thymic tumors) networks were developed to improve the management of these rare tumors according to national and international guidelines (Caplin et al. 2015, http://www.nccn.org/, http://www.reseau-gte.org, http://www.rythmic.org/). Masaoka-Koga and ITMIG-IASLC (International Thymic Malignancy Interest Group – International Association for the Study of Lung Cancer) classifications are used (Detterbeck et al. 2014).

**Surgical treatment** Complete resection is the standard of care for thymic tumors. The histological classification, stage and completeness of resection (R0) are major prognostic factors. Centers with expertise in thoracic and cardiovascular surgery are recommended. Thoracic MRI could be useful to evaluate the resectability. Surgical guidelines recommend total thymectomy, which involves removing the thymoma and the entire thymus, as well as all perithymic fat without opening the tumor capsule. Median sternotomy is an elective approach. Depending on the tumor volume or pleuro-pulmonary extension, specific and/or complementary surgical approaches can be used (for example, antero-bilateral thoracotomy with transverse sternotomy (Clamshell) and partial longitudinal sternotomy with anterolateral extension with thoracotomy (hemi-clamshell)). Complete resection may require resection of surrounding involved structures, including the pericardium, pleura, lung and even major vascular structures. Resection of suspected adenopathy is also mandatory. Minimally invasive procedures, such as video or robot-assisted thoracoscopy surgery (V- or RATS), can be used for small and/or well-encapsulated thymic tumors. In selected patients, minimally invasive techniques for thymectomy are used more frequently because they have demonstrated significant advantages in...
terms of peri-operative and esthetic outcomes (Fig. 4C,D) (Hess et al. 2016, Marulli et al. 2016).

Given the frequency of ectopic parathyroid glands in the thymus, prophylactic transcervical thymectomy is generally performed at the time of parathyroid surgery for primary hyperparathyroidism in patients with MEN1; however, its efficacy in preventing TNETs and/or improving survival has not been demonstrated (Powell et al. 2008, Welch & McHenry 2012); this is probably because the thymectomy is only partial in most patients, leaving a significant amount of thymic tissue behind. There is currently debate over whether total thymectomy (using minimally invasive techniques like VATS, RATS or subxyphoid approach) should be added to parathyroidectomy at the time of the latter. Long-term follow-up of patients with MEN1 who have undergone preventive thymectomy during parathyroidectomy is recommended. A prospective evaluation of a RATS/VATS/subxyphoid approach for complete prophylactic thymectomy in combination with cervical parathyroidectomy in patients with MEN1 is required.

Radiotherapy and medical therapy Adjuvant radiotherapy for incomplete resection and/or positive margins or systemic treatments for metastatic disease must be discussed by a multidisciplinary board and/or a dedicated network (for example, RENATEN in France). Medical treatments for unresectable/metastatic sporadic TNETs are based primarily on somatostatin analogs, chemotherapy (temozolomide/5-fluorouracil/oxaliplatin), mTOR inhibitors (everolimus) and PRRT.

Conclusion
In patients with MEN1, investigations for a thymic tumor need to be conducted and, in the case of TNETs, a potential diagnosis of MEN1 should be considered. Significant changes have occurred in the management of TNETs in the last 20 years (Table 1). The main treatment of MEN1 associated TNETs is surgery.

### Table 1  Major changes in the management of Thymic neuroendocrine tumors (TNETs) associated with MEN1 (TNETs-MEN1) that occurred in the last 20 years.

<table>
<thead>
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<th>Clinical features</th>
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<td>Male/Female (smoker or not)</td>
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<td></td>
<td>Chest CT</td>
<td>MRI and/or low dose CT scan (Thakker et al. 2012)</td>
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**Bronchial NETs**

Most MEN1-associated lesions are either frequent (hyperparathyroidism, duodeno-pancreatic-NETs, pituitary lesions, adrenal lesions) or rare, with a bad prognosis, such as TNETs. Br-NETs do not belong to either of these categories and very little is known about them. Indeed, the frequency of br-NETs in patients with MEN1 ranges from 3% to 13% and may be up to 31% (Sachithanandan et al. 2005, Goudet et al. 2011, de Laat et al. 2014, Singh Ospina et al. 2015, Bartsch et al. 2016). This large range is the result of the use of imaging findings and/or pathology as the basis for diagnosis. Two recent and large series are dedicated to the natural history of MEN1-related br-NETs (de Laat et al. 2014, Lecomte et al. 2017). In a Dutch study, br-NETs were diagnosed using either imaging alone or using pathology when available. Nevertheless, the complete diagnosis of br-NET relies on the basis of suggestive morphology and confirmatory immunophenotyping, including the expression of chromogranin A, synaptophysin and/or N-CAM by neoplastic cells. Such criteria were recently used in the French GTE registry (Lecomte et al. 2017). Fifty-one patients had developed br-NETs (4.8%; 95% confidence interval, CI = 3.6%–6.2%). The female-to-male sex ratio was 1.2 (23 men, 28 women) and several cases belonged to the same families. The median age at br-NET diagnosis was 49 ± 11 years (range = 24–66 years). Considering the frequencies of histologically proven br-NETs, very similar results were found worldwide: 4.6, 4.8, 4.9, 5.0 and 6.6% in Dutch (n = 16) (de Laat et al. 2014), French (n = 51) (Lecomte et al. 2017), US (n = 17) (Singh Ospina et al. 2015), Tasmanian (n = 6) (Sachithanandan et al. 2005) and German (n = 5) (Bartsch et al. 2016) cohorts, respectively.

Penetrance is another important clinical aspect of br-NETs. No case has been described during the first 2 decades of life. The youngest patient described in the literature was aged 20 years. The probability of developing a br-NET increases slowly with age and reaches 8.1% (95% CI = 5.9–11.0%) at 60 years (Lecomte et al. 2017). There was no evidence of the predominance of either
sex. These results were obtained when the 3 largest series were pooled (female-to-male sex ratio: 1:16) (de Laat et al. 2014, Singh Ospina et al. 2015, Lecomte et al. 2017). This conclusion was also true in the atypical carcinoid (AC) subgroup, while a recent Surveillance, Epidemiology, and End Results (SEER) program population-based study that considered all cases of sporadic and non-sporadic AC together described a predominance of women (69%) (N = 441) (Steuer et al. 2015).

The occurrence of br-NET-related clinical symptoms is rather exceptional in the GTE cohort (14%), and a similar figure was also reported in the Mayo Clinic series (23%) (Singh Ospina et al. 2015, Lecomte et al. 2017). Thus, br-NETs are mostly diagnosed using screening during the follow-up of patients with MEN1. Dyspnea, hemoptysis, cough and flushing, which are well-known br-NET-related symptoms, are useful for diagnosis if they are present (Fink et al. 2001). Several cases of br-NETs were found in the same families (Lecomte et al. 2017). Therefore, the issue of possible clusters, such as those observed for TNETS, has to be raised. It is therefore important to pay particular attention to families in which 1 or 2 cases have been already encountered. Recommendations for br-NET detection must be meticulously followed in these families. In other cases, br-NET detection is very challenging. There is no direct genotype–phenotype correlation and no other more frequent lesions from the MEN1 spectrum are associated with br-NET occurrence (Lecomte et al. 2017).

Although precise histology is a major issue in br-NETS, there are well-demonstrated inconsistencies in distinguishing between typical carcinoids (TC) and AC, between AC and large-cell neuroendocrine carcinomas (LCNEC) or between LCNEC and small-cell neuroendocrine carcinomas (SCLC). It may be difficult to assess cell size and cytological features in SCLC and LCNEC and also to recognize mitoses and necrosis among TC and AC (den Bakker et al. 2010, Volante et al. 2011, Swarts et al. 2014). Ki67 immunohistochemistry may be helpful in the differential diagnosis between the subtypes of lung NETs (Travis et al. 2004). Most br-NETs were classified as TC and AC in the GTE series; however, 5 cases of SCLC and LCNEC were also found (10%) (Lecomte et al. 2017). Until now, there have been no reports of SCLC and LCNEC in MEN1, which is probably because of the small size of the published series and the rarity of these high-grade neoplasms. It was generally regarded that MEN1-related br-NETs behave indolently, albeit with the potential for local mass effect, metastasis and recurrence after resection (Sachithanandan et al. 2005). The high frequency of smokers in this subset of patients is noteworthy and in-keeping with the epidemiology of these neoplasms in the general population (Yeh & Chou 2014). Loss of heterozygosity (LOH) at 11q13, in the

![Figure 5](https://www.erc.endocrinology-journals.org/content/24/10/254/F5.large.jpg)

**Figure 5**
Management of MEN1 patients with br-NET.

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1 NSCLC: non-small cell lung cancer
2 nodule size + morphology, clinical risk factors including age and smoking (MacMahon et al. 2017)
3 tumours that are localized close to vital structures and that would need an extensive resection if they grow
4 for staging, multiphasic chest and abdominal CT is mandatory; consider Gallium DOTA PET for non-aggressive tumours and FDG PET-CT for aggressive tumours. Bronchoscopy (+ biopsy) is mandatory for centrally located lesions. See also (Caplin et al. 2015)
region containing the MEN1 gene, has been reported to be frequent in sporadic cases of both SCLC and LCNEC (Onuki et al. 1999). Nevertheless, subsequent studies have identified the presence of silencing MEN1 mutations in only very exceptional cases of sporadic high-grade NETs (Debelenko et al. 2000). Although poorly differentiated br-NETs occur in MEN1, their cause is unknown. They must be considered because they represent 10% of MEN1-related br-NETs. The most aggressive histological tumors were clearly responsible for br-NET-related deaths (SCLC, LNEC and several cases of AC) (Lecomte et al. 2017). Several other distinctive features need to be highlighted in MEN1-related br-NETs. TC was more common than AC with a ratio of 2:1. In cases of sporadic br-NETs, this ratio ranges from 8:1 to 12:1. SCLCs account for only 5% of all MEN1-related lung tumors while SCLC is the third most frequent type of primary lung malignancy after squamous cell carcinoma and adenocarcinoma in the general population (Swarts et al. 2014). Thus, clinicians must be aware of this particular histological spectrum of lung tumors in MEN1 in order to diagnose and treat them properly knowing that when surgery was carried out, large resections were not usually required and no surgery-related deaths occurred (Lecomte et al. 2017).

Finally, these results highlight the importance of detecting br-NETs in MEN1, since 37 (72%) patients required surgery and 7 (14%) died from br-NET (Lecomte et al. 2017). Moreover, systematic screening detected br-NETs in 27% of patients with MEN1 (de Laat et al. 2014). Therefore, screening patients with MEN1 for br-NETs every 3 years from the age of 20 years seems sufficient since the doubling time of these tumors is only 4.5 years (de Laat et al. 2014). Nevertheless, published recommendations tend to propose annual imaging of the chest because of the risk of aggressive TNETs, even though they are rare (Thakker et al. 2012, de Laat et al. 2014). The optimal imaging modality is still debatable because of the cumulative radiation, which could be harmful to the vast majority of these patients. The risk of cancer induced by CT scans during childhood is now well documented (for example, brain and thyroid cancers and leukemia) (Journy et al. 2014). There are also strong recommendations to replace CT scans with other modalities, including MRI during the follow-up of presymptomatic patients (Pearce et al. 2012). MRI could be a good alternative, even though it is not recommended for chest screening. A study that compares MRI with CT scans among MEN1 patients is required in order to determine which is best (Singh Ospina et al. 2015).

The management of br-NETs in patients with MEN1 classically follows that of sporadic br-NETs (Fig. 5). Resection is usually recommended but small non-central lesions (tumors that are not close to vital structures and that would not need an extensive resection if they slightly grow) can probably be followed without affecting mortality. The type of resection depends on the location of the tumor and should be as lung-sparing as possible, including the use of endobronchial resections when feasible (Brokx et al. 2015, Caplin et al. 2015).

In conclusion, br-NETs can be fatal. MEN1-related br-NETs must be detected during a well-designed follow-up and histological characterization must be performed.

Declaration of interest
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