Neuroendocrinology

Neuroendocrinology (DOI:10.1159/000464292)
(Accepted, unedited article not yet assigned to an issue)

Advanced Release: February 25, 2017

Received: December 14, 2016
Accepted after revision: February 19, 2017

ENETS Consensus Guidelines for Standard of Care in Neuroendocrine Tumours: Surgery for Small Intestinal and Pancreatic Neuroendocrine Tumours

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Abstract

Small intestine and pancreas are among the most frequent abdominal sites of origin of neuroendocrine tumours. Distinctive features of these forms are represented by the relative low incidence and the wide heterogeneity in biological behavior. In this light, it is difficult to standardize indications for surgery and the most appropriate approach. It would be helpful for surgeons managing patients with these tumours to have guidelines for surgical treatment of small intestinal neuroendocrine tumours (siNETs) and pancreatic neuroendocrine tumours (PanNETs). The proposed guidelines represent a consensus of the working group of the European Neuroendocrine Tumor Society (ENETS).

Background

Pancreas and small intestine are the most frequent sites of origin for neuroendocrine neoplasms of the gastro-entero-pancreatic region [1]. Radical surgical resection represents the only hope of cure for these tumours. As the wide heterogeneity of neuroendocrine lesions, surgical management comprises several options ranging from conservative, minimally invasive procedures to extensive resection that may include also vascular and multivisceral resections.

The low incidence of neuroendocrine tumours, the wide heterogeneity in terms of grading and staging as well as the variety of treatments offered during postoperative course are the main reasons behind the lack of evidence on different aspects of surgical treatment. In view of the higher incidence compared with other sites of origin, it would be helpful for surgeons managing small intestinal neuroendocrine tumour (siNETs) and pancreatic neuroendocrine tumours (PanNETs) to have specific guidelines.

Methods

During the Advisory Board Meeting of the European Neuroendocrine Tumor Society (ENETS) held in Antibes, France, in 2015, a consensus meeting on this topic was organized. The working group identified 8 issues of clinical interest: preoperative assessment before surgery, definition of primary tumour resectability, surgery for localized disease, role of lymphadenectomy, surgery for locally advanced disease, surgery for metastatic disease, postoperative complications, and laparoscopic approach. On these specific issues, the working group set up 21 questions and worked on the answers. For this purpose a systematic literature search was conducted using PubMed, Embase and Cochrane Library databases employing the terms: "pancreatic neuroendocrine tumours"[All Fields] AND "surgery"[All Fields]"; "small intestinal neuroendocrine tumours"[All Fields] AND "surgery"[All Fields]"; "carcinoid tumours"[All Fields] AND "surgery"[All Fields]". The PubMed function “related articles” was used to broaden each search, and the reference list of all potentially eligible studies was analysed. All titles and abstracts of the considered studies were analysed by the group in order to select those focusing on surgical management of siNETs and PanNETs. All the statements were shared and approved by the working team.

1. Preoperative assessment before surgery

1.1 What should be the minimal ENETS standard of care for preoperative assessment before surgery for siNETs?

Functioning forms account for around the 20% of all siNETs [2]. An accurate assessment of previous and current medical history should be always performed for investigating the presence of carcinoid syndrome-related symptoms. Levels of 24-hour urinary 5-hydroxy indole acetic acid (5-HIAA) have to be evaluated despite the absence of specific symptoms. At least a high-quality abdominal imaging technique with frontal slices (computed tomography [CT] or magnetic resonance [MR]) is required before surgery. The imaging assessment should precise the primary sites (30% multiple) often small in size, LN-stage and presence of hepatic nodules [2, 3]. Both CT and MR showed similar rate of sensitivity in staging disease preoperatively but CT seems to be more effective in detecting anatomical details that matter from a surgical standpoint (i.e. vascular invasion, lymph node involvement)[4, 5]. MR either in T2 sequences or with DW sequences could better detect hepatic nodules [6]. Somatostatin receptor imaging modalities (somatostatin receptor scintigraphy [SRS] or positron emission tomography [PET] scanning with 68Gallium) are needed preoperatively for better staging tumours in terms of occult metastases and/or extra-abdominal disease [2]. Both morphological and functional imaging usually underestimate disease stage [4, 7]. Moreover, echocardiography should be routinely performed in order to rule out carcinoid heart disease before any surgical intervention. Since the reported correlation between siNETs and other colorectal neoplasms a colonoscopy may be included in the preoperative work-up [8]. A meticulous intraoperative exploration of all abdominal cavity and the palpation of the whole jejunum and ileum are superior to all imaging modalities and should be systematically executed [4, 5].

Statement: Preoperative assessment before elective surgery for siNETs should include a CT-scan and a SRS or PET/CT with ^{68}Gallium. Levels of 24-hour urinary 5-hydroxy indole acetic acid (5-HIAA) as well as echocardiography.

1.2 What is the best procedure for detecting multifocal siNETs?

Multifocal siNETs occur in around 20-30% of patients and their correlation with a poorer prognosis is controversial[9-12]. CT and MR have demonstrated a very low accuracy in detecting multifocal siNETs [9]. An accurate and systematic intraoperative bidigital palpation of the entire small intestine from the Treitz ligament to the cecal valve bowel has been demonstrated to be effective in detecting multifocal siNETs compared with all preoperative imaging modalities [9-12]. Exploration has to be performed before and after digital compression, as tumour may not be visible by simple inspection [12, 13]. Other perioperative modalities as MR-enterography and video capsule endoscopy (VCE) were associated with a high identification rate for primary siNETs [13] but their routine use preoperatively is not justified. Intraoperative enteroscopy has been proposed for a better detection of small nodules, but it has been abandoned because of increase rate of major postoperative complications[14, 15].

Statement: Intraoperative bidigital palpation of the entire ileojejunal bowel is the best procedure for detecting multifocal siNETs

1.3 What should be the minimal ENETS standard of care for preoperative assessment before surgery for PanNETs?

An accurate preoperative staging for PanNETs is essential for determining the stage of disease, the most appropriate surgical resection, and the relationship between primary tumour and peripancreatic vessels. Both CT scan and MR are accurate in the detection of the primary tumor [16]. Functional imaging (SRS and PET/CT with 68Gallium) is essential for excluding extra-abdominal disease as well as for a more accurate assessment of occult liver metastases not seen at high-quality imaging techniques [16]. Small PanNETs < 2 cm (i.e. insulinomas) should be investigated for their relationship with the main pancreatic duct in order to evaluate the feasibility of enucleation[17, 18]. MR-cholangiopancreatography and endoscopic ultrasound (EUS) are the most effective modalities for assessing the relationship between the nodule and the pancreatic duct and should be included in the preoperative work-up when enucleation is warranted [17, 18]. Possible vascular involvement can occur in the presence of aggressive PanNET. In particular an infiltration of the superior mesenteric

vessels and/or the common hepatic artery needs to be precisely investigated in order to define a possible vascular resection or excluding patients from an upfront surgery. CT scan is the most accurate high-quality imaging procedure for studying the vascular involvement in the presence of pancreatic malignancies and it needs to be routinely included in diagnostic work-up before surgery [19].

Statement: Preoperative assessment before surgery for PanNETs should include a CT-scan and a SRS or PET/CT with ^{68}Gallium. MR-cholangiopancreatography and EUS should be included in the preoperative work-up when enucleation is warranted.

2. Definition of primary tumour resectability

2.1 Which patients should be considered unresectable for their primary siNET? Is this always related to LN or fibrotic desmoplastic reaction and/or invasion of superior mesenteric vessels toward retroperitoneum?

Primary siNETs are usually small lesions that can be easily resectable. An adequate oncological surgical resection is usually influenced by the presence of tumour mesenteric deposits and lymph node metastases that may be surrounded by massive fibrotic reaction. Approximately 5% of patients affected by siNETs exhibit miliary seeding in the intra-abdominal cavity equivalent to peritoneal carcinomatosis (PC) [20]. Many of these patients develop a “frozen abdomen”, particularly in the pelvis, despite the absence of bulky liver metastases [21]. The presence of large tumour deposits is associated with an increased risk of failure of radical resection as well as a high risk of disease progression also when surgery succeeds [20, 22]. Nevertheless, dissection of mesenteric metastases is possible even when siNETs are deemed inoperable unless tumour growth completely surrounded the mesenteric vessel root or extended retroperitoneally [3, 20, 23]. In this light, primary siNETs could be classified as i) “resectable” in the absence of large mesenteric tumor deposits close to the mesenteric root, ii) “borderline resectable” when large mesenteric tumor deposits are present without major involvement of the mesenteric vessel root and/or retroperitoneum, and iii) “locally advanced or irresectable” when mesenteric tumor deposits surround the mesenteric vesselsroot or extend

retroperitoneally. Recent update on the treatment of patients with siNETs and PC stipulates to take into account not only the PC resectability but also the presence of liver metastases and the degree of the resectability of hepatic disease that for most of the patients will determine the prognosis [20].

Statement: SiNETs with mesenteric tumour deposits surrounding the mesenteric vessel root or extend retroperitoneally should be considered unresectable. SiNETs with large mesenteric tumor deposits without involvement of the mesenteric vessel root should be regarded as "borderline resectable".

2.2 Which is the definition of unresectable primary PanNETs?

Currently two different staging systems for PanNETs have been proposed by ENETS and by the American Joint Committee on Cancer (AJCC) [24, 25]. The AJCC classification distinguishes pT3 from pT4 by the recognition of major vascular invasion [25]. Nevertheless, this distinction is not sufficiently detailed for considering all T4 PanNETs as unresectable tumours. Peripancreatic vessels (superior mesenteric vein [SMV], superior mesenteric artery [SMA], celiac axis [CA] and common hepatic artery [CHA]) involvement is the most important determinant of likelihood of radical surgical resection. A possible classification of pancreatic tumour resectability can be that proposed for ductal adenocarcinoma [26]. In this light three different conditions are identified: i) "resectable" PanNET when normal tissue plane is present between tumour and SMA and/or CA and/or CHA, ii) "borderline resectable" PanNET when abutment is present between tumour and SMA and/or CA and/or CHA, iii) "locally advanced" PanNET in the presence of SMA and/or CA and/or CHA encasement. Involvement of SMV is not a criterion for unresectability except in the presence of vein occlusion, providing that the involved segment is manageable.

Statement: PanNETs with SMA and/or CA and/or CHA encasement as well as those with SMV occlusion should be considered unresectable. PanNETs with SMA and/or CA and/or CHA abutment as well as those without segmental SMV occlusion should be regarded as "borderline resectable".

3. Surgery for localized disease

3.1 Should all of the siNETs be operated? Is there any place for wait and see attitude?

Because of their inconspicuous size and deep submucosal location, primary siNETs are rarely incidentally diagnosed or before metastases have developed, and thus, patients often present with advanced disease [27]. Occult lesions can be early detected with aggressive screening among patients with a family history of siNETs [27]. More than 80% of these patients have multifocal disease and one third present a stage III disease. Moreover, nearly half of patients with siNETs<10 mm show lymph node metastases [28]. In this light, all siNETs should be regarded as aggressive disease and therefore managed operatively with adequate surgical resection and lymphadenectomy.

Statement: All localized siNETs, even when small and incidentally discovered, require radical surgical resection with adequate lymphadenectomy irrespective of the absence of lymphadenopathy or mesenteric involvement

3.2 Should all small asymptomatic PanNETs be operated in the absence of metastases and local signs of invasiveness?

In the last decade a dramatic increase in the diagnosis of small, asymptomatic PanNETs has been observed [29, 30]. In particular it has been estimated that incidence of PanNETs < 2 cm in size increased by 710% over a 20-year period [29]. Moreover, tumour size and incidental diagnosis are powerful predictors of aggressiveness among PanNETs [31, 32]. A tumor size between 1.5 and 2 cm seems to be the most accurate cut-off for distinguishing between indolent and aggressive forms [33]. A conservative management of small, asymptomatic PanNETs consisting of active imaging-based surveillance seems to be safe in the short-term [34]. A watchful strategy instead of surgical treatment should be proposed at least in selected patients. Surgical resection should be still recommended in young and healthy patients as the absence of available data on long-term follow-up. On the other hand, young patients affected by MEN1 syndrome who have non-functioning PanNETs < 2cm can be safely enrolled in an observational protocol. In this subgroup of patients, a watchful strategy has been well established and long-term follow-up demonstrated the safety of this approach [35-37].

In all the cases, surgery is the treatment of choice, also in the presence of small asymptomatic PanNETs when the main pancreatic duct is involved [38]. Even in small PanNETs pancreatic duct involvement is associated with multiple unfavourable clinicopathological features (e.g. higher histological grade, nodal metastases, and higher recurrence rates).

Statement: Conservative management should be considered for asymptomatic, nonfunctioning PanNETs < 2 cm for in patients affected by MEN1 and for selected patients (significant comorbidity, advanced age) with the sporadic form. For these tumours, surgery is still the treatment of choice in young and healthy patients and in the presence of MPD involvement and/or other signs of local invasiveness (e.g. dilation of the main pancreatic duct, jaundice, vascular and/or nodal involvement involvement).

3.3 When is it appropriate to perform atypical, parenchyma-sparing, pancreatic resection for PanNETs (e.g. enucleation, central pancreatectomy)?

Parenchyma-sparing pancreatic resections represent alternative options for the operative management of small PanNETs. Central pancreatectomy for PanNETs located in the pancreatic neck minimizes the risk of developing pancreatic insufficiency as compared with extended distal pancreatectomy [39, 40]. Similarly, enucleation of PanNETs allows resecting the tumour sparing the whole pancreatic gland [41]. Main limitations of these techniques are the risk of inadequate surgical margin clearance and the absence of lymphadenectomy. These operations are associated with a high rate of postoperative complications, in particular pancreatic fistula, and similar mortality risk as compared with standardized pancreatic resections [42-44]. Oncological safety of these procedures is not well defined as the absence of comparable data in literature [44]. Moreover, surgical treatment of small PanNETs is significantly limited by emerging evidence on the value of a “wait and see” attitude toward these forms. Consequently, indications of parenchyma-sparing pancreatic resections should be now suggested only for small insulinomas [45, 46] or for selected patients affected by small PanNETs when conservative management is contraindicated (e.g. young patients or patients who refuse observational management).

Statement: indications of parenchyma-sparing pancreatic resection should be limited to insulinomas and small PanNETs < 2 cm when a conservative management is contraindicated.

4. Role of lymphadenectomy

4.1 What is the minimal number of lymph nodes to be harvested during resection for siNETs? Does an extended lymphadenectomy play a role in the prognosis of patients with siNETs?

Around 80-88% of patients with siNETs has lymph node metastases at the time of initial diagnosis [3, 9, 12, 47-49]. A systematic lymphadenectomy (at least > 8 resected nodes) is associated with a significantly better survival compared with selective lymphadenectomy [50, 51]. It should be pointed out that these findings were not corroborated by other studies [3, 47]. The optimal cut-off of lymph nodes to be resected during surgery for siNETs is still controversial as the absence of standardized surgical procedures. Lymphadenectomy is not correlated with the length of surgical specimen after small bowel resection [3]. The “pizza pie” resection rule, following which the resection of a large intestinal segment is required, should be abandoned, because it predominantly removes intestine rather than lymph nodes [3]. A reverse lymphadenectomy followed by small bowel resection, possibly extended to right colon, allows reducing the length of surgical resection warranting an appropriate lymphadenectomy in a small intestinal-sparing strategy [3, 12, 28, 49, 52]

Statement: An adequate and systematic lymphadenectomy (at least 8 nodes) limiting the length of intestinal loop to be resected is always recommended for siNETs.

4.2 Which is the role of lymphadenectomy during pancreatic resection for PanNETs? Which is the minimum number of lymph nodes harvested required according to the type of pancreatic resection performed?

Lymph node involvement is one of the most powerful prognostic factors after surgical resection for PanNETs [53-58]. The optimal number of lymph nodes to be resected during pancreatic resection for PanNETs is unknown [57]. On the other hand, different variables including tumor size, pancreatic head localization, tumor grade, and age have been associated with an increased risk of lymph node

metastases [54, 55, 57]. Moreover, several studies focused on pancreatic ductal adenocarcinoma demonstrated an increased risk of recurrence when the number of harvested lymph nodes after pancreaticoduodenectomy is below 12 [59, 60]. Therefore, in the presence of a PanNETs > 2 cm located in the pancreatic head, it is recommended to perform an adequate lymphadenectomy including at least peripancreatic nodes (station 13 and 17) and SMA nodes (station 14).

Statement: During pancreatectomy for PanNETs > 2 cm a regional lymphadenectomy should be routinely performed. Number of harvested/examined lymph nodes for PanNENs is not yet properly addressed but at least 12 lymph nodes should be removed

4.3 Is there a role for nodal sampling during atypical pancreatic resection for PanNETs?

Atypical pancreatic resections (e.g. enucleation and central pancreatectomy) achieve a significantly lower lymph node sample than standardized resection [61]. The risk of lymph node metastases is significantly associated with tumour size and also patients with small PanNETs have a measurable risk of lymph node involvement [55, 57]. This indicates that during atypical pancreatic resection for small PanNETs a nodal sampling may be routinely justified for improving disease stage, especially in the presence of suspicious lymph nodes. Intraoperative demonstration of nodal involvement by frozen section procedure should induce the surgeon to perform a standardized pancreatic resection according to tumour localization instead of performing an atypical procedure.

Statement: Nodal sampling and frozen section during atypical pancreatic resection is recommended especially in the presence of suspicious lymph nodes.

5. Surgery for locally advanced disease

5.1 Which is the role of surgery for borderline resectable or locally advanced siNETs? Is there any place for two step surgery?

The local effects of primary tumor growth and the development of mesenteric nodal disease with associated fibrosis may complicate siNETs. The mesenteric mass can cause acute or chronic intestinal obstruction and/or localized intestinal ischemia. These complications are often associated with

significant morbidity in addition to the release of peptides leading to the carcinoid syndrome [23]. In experienced centers, a complete resection of primary tumor and regional mesenteric nodal metastases can be achieved in up to 80% of cases [7, 12, 50]. Only in a minority of patients, large mesenteric mass lesions cannot be completely resected or debulked [7]. Patients with symptoms due to mesenteric involvement from siNETs should be always referred to specialized centers for surgical exploration, especially for reoperations. Resection of large mesenteric metastases may not be possible or appropriate, especially in an emergency setting when performed by surgeons without adequate experience. Radical resection or debulking surgery provide relief of the obstructive symptoms[7, 62, 63]. Moreover, surgical clearance of mesenteric disease seems to be associated with better survival [7].

Statement: Radical or palliative surgical resection is recommended for symptomatic patients with borderline resectable or locally advanced siNETs

5.2 Which is the role of surgery for borderline resectable or locally advanced PanNETs? Which is the role of surgery for PanNETs in the presence of nearby organ invasion (i.e. stomach, colon, adrenal gland, and kidney)?

Localized, non-metastatic, PanNETs usually do not exhibit an aggressive behaviour with signs of local invasiveness. Therefore, pancreatic resection for PanNETs with vascular involvement has been rarely described [64, 65]. Usually, pancreatic surgery with vascular reconstruction in the presence of SMV abutment is safe and associated with acceptable outcome. Nevertheless, data are still lacking to confirm the value of vascular reconstruction in the presence of SMA or CA invasion. Multivisceral resection in the presence of nearby organs invasion is associated with a poorer survival when compared with standard resection[66-69]. These findings indicate a more aggressive behaviour of PanNETs when invading other organs. Nevertheless, a multivisceral resection should be contemplated only for selected patients with low-grade-intermediate (G1-G2) neoplasms.

Statement: Selected patients with low-grade-intermediate (G1-G2) PanNETs without distant metastatic disease, may benefit from an extended multivisceral pancreatic resection with or

without combined vascular reconstruction. Surgery is generally contraindicated for locally advanced PanNETs when a macroscopic radical resection cannot be achieved.

6. Surgery for metastatic disease

6.1 Which is the role of surgery in the presence of siNETs or PanNETs with resectable liver metastases?

Liver metastases occur in the 40-45% of siNETs and PanNETs [70, 71]. Surgery may play a role also in the presence of metastatic disease, because the majority of neuroendocrine tumours have a relatively indolent behaviour and the liver is often the only site of metastases. An accurate selection of patients is of paramount importance before considering any surgical approaches in patients with liver metastases. Firstly, high-grade tumours (G3) should be excluded by upfront surgical approach in the presence of liver metastases. The risk of recurrence after radical surgery in patients with neuroendocrine liver metastases is significantly higher for high-grade tumours as compared with low-, intermediate forms [72, 73]. Secondly, the presence of extra-abdominal disease needs to be preoperatively ruled out by high-quality imaging techniques and functional imaging (PET/CT with ^{68}Gallium) [74]. Lastly, the distribution of liver metastases in patients represents another a critical issue. Patterns of localization of neuroendocrine liver metastases have been classified into three categories: single metastasis of any size (type I); isolated metastatic bulk accompanied by smaller deposits, with both liver lober always involved (type II); disseminated metastatic spread, with both liver lobes always involved (type III) [75]. Radical resection for patients with type I metastatic siNETs or PanNETs is associated with good outcomes and significantly better survival rates when compared to patients who undergo medical treatments alone [73]. On the other hand, a surgical approach for patients with type II liver metastases is more controversial. For this pattern of metastatization, a two-step approach, which includes a resection of left metastases associated with a right portal vein ligation followed by right hepatectomy, may be proposed [70, 71, 76, 77].

Statement: Radical resection for resectable or potentially resectable neuroendocrine liver metastases is suggested in selected patients with well differentiated (G1-G2)tumours in the absence of extra-abdominal metastatic disease

6.2 When should the primary siNET be operated in the presence of unresectable liver metastases?

Resection of primary siNET in the presence of unresectable liver metastases plays an important role in preventing complications related to bowel obstruction or intestinal ischemia and improving symptoms associated with hormonal secretion [78-80]. If symptomatic for occlusion surgery is the only way to achieve symptoms relief. Primary siNET resection seems to be also associated with a prolonged overall survival when associated with an extensive mesenteric dissection [78]. Nevertheless, the lack of prospective, randomized clinical trials, does not allow firm conclusions on the potential benefit in terms of survival for primary siNET resection.

Statement: In the presence of unresectable liver metastases, palliative primary siNET resection with adequate lymphadenectomy should be considered to prevent or relieve symptoms related to bowel obstruction.

6.3 When should the primary PanNETs be operated in the presence of unresectable liver metastases?

The role of primary PanNETs resection in the presence of unresectable liver metastases is still controversial. Apart from rare functioning forms, primary PanNETs of the pancreatic body/tail usually are not associated with specific symptoms. As regards of pancreatic head PanNETs, the possible occurrence of obstructive complications such as jaundice or duodenal occlusion may be managed endoscopically or by surgical bypasses. In this light, the value of palliative surgery in metastatic PanNETs seems to be considerably limited. Nevertheless, data from retrospective studies demonstrated that primary PanNET resection may increase survival [73, 81-85]. A possible mechanism is related to an enhanced response to peptide receptor radionuclide therapy (PRRT) given the less tumour burden after primary tumour removal [83]. Palliative PanNET resection should be reserved to patients with well differentiated tumours (G1-G2). Moreover, the rate of complications after pancreaticoduodenectomy and the elevated risk of liver abscess after ablative liver-directed

therapies related to the presence of biliary anastomosis, could affect significantly the patients` quality of life and outcome. In this light, palliative resection of PanNETs located in the pancreatic head should not be recommended.

Statement: In the presence of unresectable liver metastases, a routine palliative primary PanNET resection, especially a pancreaticoduodenectomy, is not justified. In selected patients with well-differentiated tumours located in the pancreatic body-tail, primary PanNET resection may be considered.

6.4 Which is the role of liver transplantation in the presence of siNETs or PanNETs with unresectable liver metastases?

Liver transplantation is an alternative option for the management of patients with unresectable neuroendocrine liver metastases. A strict patient selection is mandatory before considering liver transplantation. Selection criteria include the absence of extra-hepatic disease, histological confirmation of a well-differentiated (G1-G2, Ki67<10%) neuroendocrine tumour, previous removal of primary tumour, metastatic diffusion <50% of the total lover volume, stable disease to therapies for at least 6 months prior to transplant consideration, and age < 60 years [86]. Exploratory laparotomy or laparoscopy to detect peritoneal deposits may be considered [87, 88]. The failure to detect the primary tumour before transplantation should not be considered as an absolute contraindication[89]. Only if these strict criteria are met, patients will benefit from liver transplantation, since they have a significant better survival when compared with those who undergo alternative medical and interventional treatments [86, 89].

Statement: Liver transplantation for unresectable neuroendocrine liver metastases may be proposed to highly selected patients according to strict clinical and pathological criteria.

7. Postoperative complications

7.1 What is the minimal acceptable rate of postoperative complications after surgery for siNETs?

Surgery for siNETs can be very challenging since most patients already have a gross nodal involvement or metastases at diagnosis. The rate of surgical complications has been reported to be

between 7.5 to 30% with a mortality rate of 1-1.5% [12, 48, 50]. Difference in terms of postoperative morbidity and mortality rates between high-volume and low-volume centers may not be firmly evaluated [48]. Most of patients are treated in low-volume institutions, usually in emergency setting due to intestinal complications, and they are generally referred to high-volume hospitals for more extensive resection.

Statement: Minimal acceptable rate of postoperative complications after surgery for siNETs is less than 30% with a mortality rate of less than 1.5%

7.2 What is the minimal acceptable rate of postoperative complications after surgery for PanNETs?

Pancreatic surgery is demanding and associated with a high risk of morbidity and mortality. High-volume of pancreatic resections is a crucial criterion for having an acceptable risk of postoperative complications and surgical-related deaths [90]. Additionally, it should be pointed out that pancreatic surgery for PanNETs is associated with a higher risk compared with other pancreatic malignancies [91, 92]. Patients with PanNETs have usually potential risk factors for pancreatic fistula such as a soft pancreatic texture and a not dilated main pancreatic duct. Rates of postoperative complications are classified according to the type of pancreatic resection. For standardized pancreatic resection the rate of postoperative complications is around 30-50% with a mortality risk for pancreaticoduodenectomy and distal pancreatectomy less than 5% of and less than 1%, respectively [91, 93-95].

Statement: Minimal acceptable rate of postoperative complications after surgery for PanNETs is 50% with a mortality rate of 5% for pancreaticoduodenectomy and 1% for distal pancreatectomy

8. Laparoscopic approach

8.1 What is the place of laparoscopy or minimal-invasive surgery in patients with siNETs? Is there a role of laparoscopic approach in the presence of liver metastases?

The role of laparoscopic approach for siNETs resection has been poorly investigated. Laparotomy is usually the approach of choice, because it allows an optimal exploration of the entire abdominal cavity and vascular control at the origin of superior mesenteric vessels [12, 96]. A laparoscopic resection

could be attempted only in the absence of gross lymph nodal masses or lymph nodes around the superior mesenteric artery axis, which might predict the impossibility of complete nodal resection [96]. It has also be ensured when choosing a laparoscopic approach that the small bowel can be bidigitally palpated from the Treitz ligament to the coecum to detect multifocal siNETs. Under these circumstances, laparoscopic hepatectomy for neuroendocrine liver metastases from siNETs may be a valuable option for reducing the risk of blood loss and shortening the length of stay [97].

Statement: The role of laparoscopic approach for siNETs should be limited to early forms without gross nodal involvement irrespective of the presence of liver metastases.

8.2 Which are the criteria (tumor size, localization, etc.) for defining laparoscopy or minimal-invasive surgery as the approach of choice for PanNETs?

Minimally invasive pancreatic resection has gained widely acceptance in the last decade [98]. Several pancreatic procedures such as distal pancreatectomy, enucleation, and central pancreatectomy may be now safely performed laparoscopically or robotically. The laparoscopic, including robot-assisted, approach is associated with a lower blood loss, a lower overall complication rate, and a shorter length of hospital stay [98]. Nevertheless, there is a substantial lack of data on oncological outcomes.

Statement: *Minimally-invasive* pancreatic resection of localized PanNETs of the body/tail can be considered. The minimally invasive approach should always warrant the oncological principles, including adequate lymphadenectomy and clearance of surgical margins.

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Neuroendocrinology (*International Journal for Basic and Clinical Studies on Neuroendocrine Relationships*)
Journal Editor: Millar R.P. (Edinburgh)
ISSN: 0028-3835 (Print), eISSN: 1423-0194 (Online)
www.karger.com/NEN