REVIEW

Surgical treatment of pancreatic endocrine tumors in multiple endocrine neoplasia type 1

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Surgical approaches to pancreatic endocrine tumors associated with multiple endocrine neoplasia type 1 may differ greatly from those applied to sporadic pancreatic endocrine tumors. Presurgical diagnosis of multiple endocrine neoplasia type 1 is therefore crucial to plan a proper intervention. Of note, hyperparathyroidism/multiple endocrine neoplasia type 1 should be surgically treated before pancreatic endocrine tumors/multiple endocrine neoplasia type 1 resection, apart from insulinoma. Non-functioning pancreatic endocrine tumors/multiple endocrine neoplasia type 1 >1 cm have a high risk of malignancy and should be treated by a pancreatic resection associated with lymphadenectomy. The vast majority of patients with gastrinoma/multiple endocrine neoplasia type 1 present with tumor lesions at the duodenum, so the surgery of choice is subtotal or total pancreatoduodenectomy followed by regional lymphadenectomy. The usual surgical treatment for insulinoma/multiple endocrine neoplasia type 1 is distal pancreatectomy up to the mesenteric vein with or without spleen preservation, associated with enucleation of tumor lesions in the pancreatic head. Surgical procedures for glucagonomas, somatostatinomas, and vipomas/multiple endocrine neoplasia type 1 are similar to those applied to sporadic pancreatic endocrine tumors. Some of these surgical strategies for pancreatic endocrine tumors/multiple endocrine neoplasia type 1 still remain controversial as to their proper extension and timing. Furthermore, surgical resection of single hepatic metastasis secondary to pancreatic endocrine tumors/multiple endocrine neoplasia type 1 may be curative and even in multiple liver metastases surgical resection is possible. Hepatic trans-arterial chemo-embolization is usually associated with surgical resection. Liver transplantation may be needed for select cases. Finally, pre-surgical clinical and genetic diagnosis of multiple endocrine neoplasia type 1 syndrome and localization of multiple endocrine neoplasia type 1-related tumors are crucial for determining the best surgical strategies in each individual case with pancreatic endocrine tumors.

KEYWORDS: MEN1; Pancreatic Tumors; Endocrine Tumors; Pancreatic Endocrine Tumors; Neuroendocrine Tumors.

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INTRODUCTION

Pancreatic neuroendocrine tumors (PETs) originate from pancreatic islet tissue. Pancreatic endocrine tumors may produce clinical symptoms as a result of excessive production of one or more hormones such as gastrin, insulin, somatostatin, glucagon, and vasoactive intestinal polypeptide (functioning PETs) or may be silent, producing only pancreatic polypeptides (non-functioning PETs).

Multiple endocrine neoplasia type 1 (MEN1) is a complex inherited condition, which may comprise up to 20 different types of endocrine and non-endocrine tumors, although the three most prevalent conditions are hyperparathyroidism, PETs, and pituitary tumors (1). MEN1 leads to increased morbidity and mortality rates, mainly as a result of PETs and thymic carcinoids (1,2).

No potential conflict of interest was reported.

PETs/MEN1 VERSUS S-PETs

The PETs associated with MEN1 (PETs/MEN1) may differ markedly from sporadic PETs (S-PETs) and are characterized by: (i) an earlier disease onset; (ii) a propensity to present higher risk for malignancy; (iii) multiple tumor lesions scattered throughout the pancreas and duodenum, instead of a single pancreatic nodule as in S-PETs; (iv) variable hormone production; (v) most patients having a familial history of PETs; and (vi) most cases (~90%) harboring an inactivating germline mutation in the *MEN1* tumor suppressor gene (1). Based on the clinical differences between PETs/MEN1 and S-PETs, distinct surgical approaches are used for each of these conditions.

Surgical treatment of tumor lesions in PETs/MEN1 may be controversial but its rationale is based on cure of the clinical syndrome and avoidance of malignant tumor progression (2).

In MEN1 patients, primary hyperparathyroidism is frequently the first clinical manifestation and is usually the first condition to be surgically treated. This was recently verified in a large MEN1 family caused by a founding *MEN1* gene mutation (3,4). The reduction in calcium/parathyroid hormone serum levels after total parathyroidectomy followed by

parathyroid auto-implant in patients with MEN1 is beneficial to the metabolic status, but it also leads to decreasing secretion of several hormones, such as gastrin, which in turn may cause a significant improvement of the clinical symptoms secondary to the hormonal excess (5–7). Parathyroidectomy in MEN1 should therefore be performed before operation for PETs, apart from in insulinoma.

As mentioned, surgical strategies applied to PETs/MEN1 differ greatly from the usual approaches used in patients with S-PETs. Clinical and genetic diagnosis of MEN1 should be made or ruled out before surgery in each patient with MEN1, as reported previously (3,8). This procedure will allow the identification of the best surgical approach to each individual case of PET, which may potentially lead to lower morbidity and mortality rates in patients with PET-associated MEN1.

We also performed methodical screening for the *MEN1* tumor suppressor gene in our MEN1 families, which should allow the early diagnosis and treatment of MEN1 in relatives carrying *MEN1* germline mutations and a trend towards lower morbidity rates (9).

PREOPERATIVE EVALUATION

Computed tomography, magnetic resonance imaging, and ultrasonography can miss PETs<1 cm. Octreotide scintigraphy is an efficient diagnostic tool but this depends on the size of the lesion and the presence of somatostatin receptors in the tumor cells. Recently, gallium-labeled somatostatin analog peptide has been used to detect MEN1-related tumors (10).

Endoscopic ultrasonography is the most useful tool for tumor diagnosis and localization in PETs/MEN1, as well as for depiction of the anatomic relationship with the main pancreatic duct, which is important for the proper surgical treatment. Endoscopic ultrasonography is able to detect PETs<1 cm, allowing early diagnosis (Figure 1). Invasive techniques for the diagnosis and localization of gastrinomas or insulinomas have been reported, although their accuracy has not been reproduced in all centers (11).

Furthermore, in our experience, intraoperative palpation, inspection, and ultrasonography are efficient tools to localize most lesions (11).

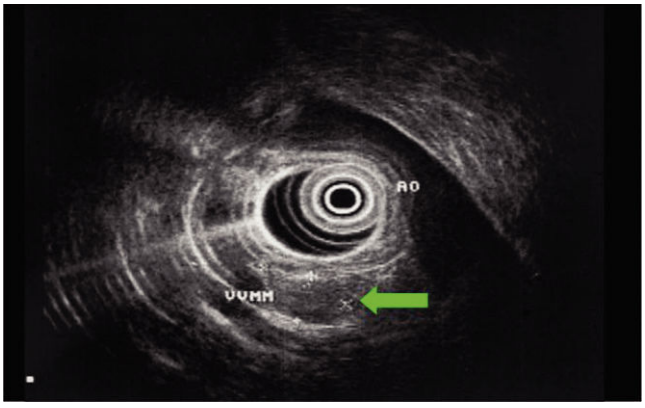

Figure 1 - Endoscopic ultrasonography. Arrow shows a small pancreatic neuroendocrine tumor.

NON-FUNCTIONING PETS

In a recent study, Goudet et al. (12) verified that PETs, including the non-functioning PETs, and thymic carcinoids are frequent causes of death in patients with MEN1.

At diagnosis, non-functioning PETs are frequently malignant, usually larger and with a worse prognosis than functioning PETs. Tumor size was positively correlated with malignancy and lesions >2.0 cm have been reported to have a higher risk for malignancy (13). In addition, other authors showed that non-functioning PETs with diameters >1.0 cm are already prone to metastasize (14). Based on these findings, pancreatic resection associated with lymphadenectomy has been recommended in these cases (14). Moreover, as liver metastases are frequently found in PETs>1.0 cm, these tumors should be carefully investigated and operated on as soon as possible (12,14). Concordantly, extended distal pancreatectomy associated with enucleation of PETs>1 cm located at the pancreatic head has also been recommended, in an attempt to prevent liver metastases (15).

Conversely, total pancreatectomy, associated or not with duodenectomy, has not been indicated because of the possible decrease in the patient's quality of life, although this surgical intervention may be used in selected PET/MEN1 patients (16).

GASTRINOMAS

The vast majority of sporadic gastrinomas are represented by single tumors located at the pancreas and the current surgical approach to these lesions is tumor enucleation.

Conversely, the majority of gastrinomas/MEN1 are multiple, asynchronic tumors mostly spread throughout the duodenum and less frequently found in the pancreas. These frequently malignant tumors (~60%) are mostly associated with multiple and small gastric carcinoids (1,3,14).

Controversies related to the surgical approach to gastrinoma/MEN1 may exist and are mostly related to the timing and extension of the surgical procedure. These tumors usually have an unpredictable course, difficult preoperative localization and present as multiple duodenal tumors. Although PETs usually lead to limited survival, some patients with metastatic PETs may survive for long periods of time with clinical treatment.

Some authors recommend surgical treatment only for cases with gastrinomas/MEN1 >3.0 cm, whereas others indicate an early surgical intervention for all gastrinoma/MEN1 patients, as soon as the diagnosis is made (14,17–19).

This controversy may be related to the fact that there appear to be two different patterns of gastrinomas in MEN1 patients: the first tend to have an indolent course with or without metastasis, whereas the second pattern is characterized by rapid tumor progression. Although there are no definite markers for the adequate identification of these two potential gastrinoma subsets, the aggressiveness of these tumors could be evaluated by the following parameters: serum levels of gastrin, tumor histological differentiation, Ki-67 positivity, a high mitotic number, and the presence of progesterone receptors, as reported recently (19).

Pancreatoduodenectomy with regional lymphadenectomy

Limited surgical resection with excision of duodenal tumors, excision of pancreatic cephalic lesions, and distal

pancreatectomy have been proposed as surgical alternatives for the treatment of gastrinomas/MEN1 (18). However, as reported in the literature and also supported by our own observations, such surgical approaches may be frequently followed by a low cure rate and a high recurrence rate.

Considering that most gastrinomas/MEN1 are located in the duodenum, a more radical surgical intervention is proposed for these patients including pancreatoduodenectomy followed by regional lymphadenectomy (17,20).

Pancreatoduodenectomy may be performed with pylorus preservation or including gastric resection (Whipple's technique). It is important to actively search for the presence of duodenal tumors even in the first 1–2 cm of the duodenum. Despite the functional advantages of the pylorus-preserving technique, it may be safer to perform Whipple's procedure in gastrinoma/MEN1 patients.

In some cases, total pancreatectomy is the treatment of choice, in an attempt at the complete removal of all tumor lesions (Figure 2). Radical resection may also be considered because the sensitivity of the methods used in detecting tumor lesions is low. Also, intraoperative gastrin measurements may be helpful to improve our capacity for determining the extent of resection (14).

INSULINOMAS

For sporadic insulinomas the diagnosis, preoperative localization, and surgical approach are well established and surgery consists of tumor enucleation (11).

In insulinoma/MEN1, the surgical management is completely different because in this condition, there are multiple tumors spread throughout the pancreas, including tumors with potential for malignancy. Enucleation is not the best treatment for these lesions because high incidences of recurrence or persistence of hypoglycemia have been reported after simple tumor enucleation.

The current therapeutic surgery for insulinoma/MEN1 is distal pancreatectomy up to the mesenteric vein with or without spleen preservation, associated with enucleation of lesions located in the head of the pancreas (Figure 3). This procedure frequently has few postoperative complications (11,14). However, in cases with major involvement of the pancreatic head, a pylorus-preserving pancreatoduodenectomy should be performed. Higher recurrence rates have been observed after surgical resection of insulinoma/MEN1, compared with sporadic insulinomas (21–23).

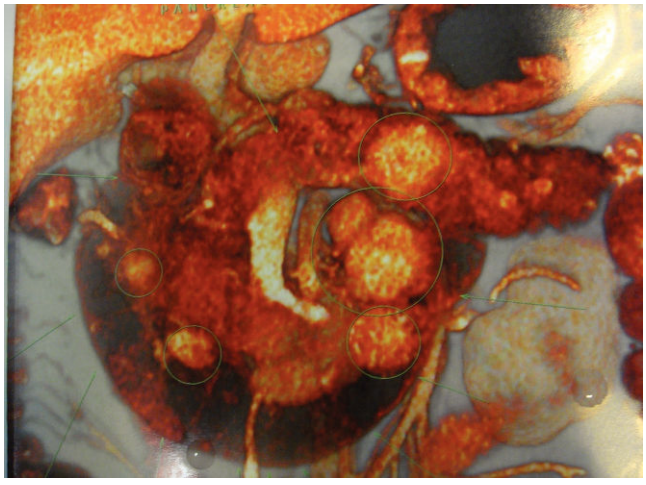

Figure 2 - Octroscan showing gastrinomas disseminated throughout the pancreas. Total pancreatectomy was performed in this case.

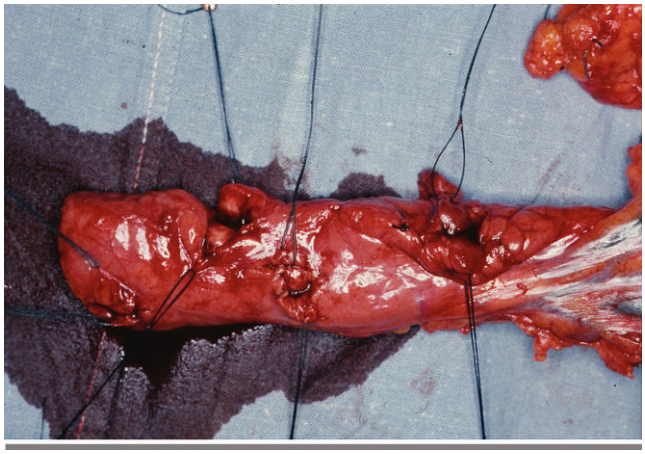

Figure 3 - Distal pancreatectomy in a patient with insulinomas associated with multiple endocrine neoplasia type 1. Eleven small tumors were found. Serum glucose returned to normal after surgery.

The confirmation of complete tumor removal is of paramount importance. Intraoperative determinations of serum glucose and insulin levels for evaluating the presence of tumor tissue left behind have been reported but their accuracy is low.

In our experience, intraoperative ultrasonography associated with monitoring of serum levels of glucose/insulin is a useful tool to confirm the completeness of tumor resection (11).

GLUCAGONOMAS, SOMATOSTATINOMAS, AND VIPOMAS

These three types of tumors occur rarely in MEN1 patients. Specific guidelines for the surgical treatment of these lesions are not currently available so the surgical procedures usually follow basically the same criteria used for non-functioning or functioning PETs described above. Most of these tumors are malignant and metastatic lesions are usually present in PETs>3 cm. Radical surgical resection is the proposed treatment for these latter lesions.

HEPATIC METASTASES

As stated by the National Comprehensive Cancer Network guideline and the consensus guidelines by the European NET Study Group: surgical treatment is the most effective therapeutic method with which to treat hepatic metastases from PETs/MEN1 (24–26).

Surgical resection of a single hepatic metastasis may be curative. Even in cases with multiple liver metastases, surgical resection is possible. In this latter situation, portal vein embolization is used as a strategy to increase the left lobe size and metastatic lesions can then be removed in a first-stage operation (Figure 4). This procedure is useful as cytoreductive surgery in patients with a clinical syndrome that is refractory to clinical treatment. Hepatic trans-arterial chemo-embolization can also be used as an ablation tool,

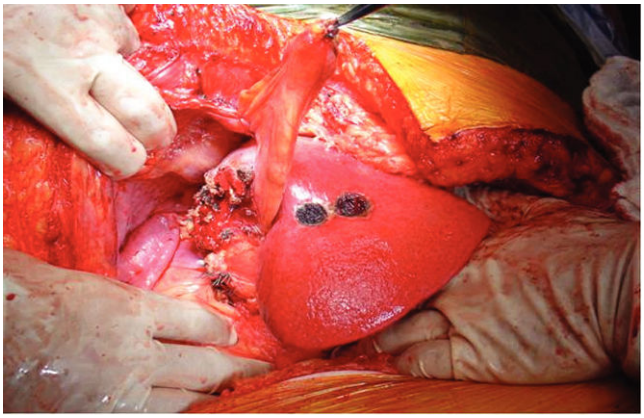

Figure 4 - Patient with bilateral liver metastases. After portal vein embolization of the right liver, an extended right hepatectomy was performed with enucleation of the left lobe metastases.

usually associated with surgical resection. Liver transplantation may also be used in selected patients (27).

CONCLUSION

Surgical strategies applied to PETs/MEN1 may greatly differ from those used in patients with S-PETs. Clinical and genetic diagnosis of MEN1 should be performed or ruled out before surgery in all patients presenting with apparently sporadic PETs. The presurgical differential diagnosis between S-PETs and PETs/MEN1 will allow surgeons to choose the best surgical approach to each individual case, aiming to lower morbidity and mortality rates, or even obtain cure, in patients with PETs associated with MEN1.

REFERENCES

1. Marx S, Spiegel AM, Skarulis MC, Doppman JL, Collins FS, Liotta LA. Multiple endocrine neoplasia type 1: clinical and genetic topics. Ann Intern Med. 1998;129(6):484–94.
2. Doherty GM, Olson JA, Frisella MM, Lairmore TC, Wells SA Jr, Norton JA. Lethality of multiple endocrine neoplasia type I. World J Surg. 1998;22(6):581–6, http://dx.doi.org/10.1007/s002689900438.
3. Lourenço DM Jr, Toledo RA, Mackowiak II, Coutinho FL, Cavalcanti MG, Correia-Deur JE, et al. Multiple endocrine neoplasia type 1 in Brazil: MEN1 founding mutation, clinical features, and bone mineral density profile. Eur J Endocrinol. 2008;159(3):259–74, http://dx.doi.org/10.1530/EJE-08-0153.
4. Lourenço DM Jr, Coutinho FL, Toledo RA, Montenegro FL, Correia-Deur JE, Toledo SP. Early-onset, progressive, frequent, extensive, and severe bone mineral and renal complications in multiple endocrine neoplasia type 1-associated primary hyperparathyroidism. J Bone Miner Res. 2010;25(11):2382–91, http://dx.doi.org/10.1002/jbmr.125.
5. Coutinho FL, Lourenço DMJr, Toledo RA, GonDeur JE, Toledo SP. Bone mineral density analysis in patients with primary hyperparathyroidism associated with multiple endocrine neoplasia type 1 after total parathyroidectomy. Clin Endocrinol (Oxf). 2010;72(4):462–8, http://dx.doi.org/10.1111/j.1365-2265.2009.03672.x.
6. Lourenco DM Jr, Coutinho FL, Toledo RA, Gonçalves TD, Montenegro FL, Toledo SP. Biochemical, bone and renal patterns in hyperparathyroidism associated with multiple endocrine neoplasia type 1. Clinics. 2012;67(S1):99–108, http://dx.doi.org/10.6061/clinics/2012(Sup01)17.
7. Coutinho FL, Lourenco DM Jr, Toledo RA, Montenegro FL, Toledo SP. Post-surgical follow-up of primary hyperparathyroidism associated with multiple endocrine neoplasia type 1. Clinics. 2012;67(S1):169–72, http://dx.doi.org/10.6061/clinics/2012(Sup01)28.
8. Toledo RA, Lourenco DM, Coutinho FL, Quedas E, Mackowiack I, Machado MC, et al. Novel MEN1 germline mutations in Brazilian families with multiple endocrine neoplasia type 1. Clin Endocrinol (Oxf). 2007;67(3):377–84, http://dx.doi.org/10.1111/j.1365-2265.2007.02895.x.
9. Lourenço DM Jr, Toledo RA, Coutinho FL, Margarido LC, Siqueira SA, dos Santos MA, et al. The impact of clinical and genetic screenings on the management of the multiple endocrine neoplasia type 1. Clinics. 2007;62(4):465–76, http://dx.doi.org/10.1590/S1807-59322007000400014.
10. Virgolini I, Ambrosini V, Bomanji JB, Baum RP, Fanti S, Gabriel M, et al. Procedure guidelines for PET/CT tumour imaging with 68Ga-DOTA-conjugated peptides: 68Ga-DOTA-TOC, 68Ga-DOTA-NOC, 68Ga-DOTA-TATE. Eur J Nucl Med Mol Imaging. 2010;37(10):2004–10, http://dx.doi.org/10.1007/s00259-010-1512-3.
11. Machado MC, da Cunha JE, Jukemura J, Bacchella T, Penteado S, Abdo EE, et al. Insulinoma: diagnostic strategies and surgical treatment. A 22-year experience. Hepatogastroenterology. 2001;48(39):854–8.
12. Goudet P, Murat A, Binquet C, Cardot-Bauters C, Costa A, Ruszniewski P, et al. Risk factors and causes of death in MEN1 disease. A GTE (Groupe d'Etude des Tumeurs Endocrines) cohort study among 758 patients. World J Surg. 2010;34(2):249–55, http://dx.doi.org/10.1007/s00268-009-0290-1.
13. Triponez F, Dosseh D, Goudet P, Cougard P, Bauters C, Murat A, et al. Epidemiology data on 108 MEN1 patients from the GTE with isolated nonfunctioning tumors of the pancreas. Ann Surg. 2006;243(2):265–72, http://dx.doi.org/10.1097/01.sla.0000197715.96762.68.
14. Imamura M. Recent standardization of treatment strategy for pancreatic neuroendocrine tumors. World J Gastroenterol. 2010;16(36):4519–25, http://dx.doi.org/10.3748/wjg.v16.i36.4519.
15. Jensen RT, Berna MJ, Bingham DB, Norton JA. Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. Cancer. 2008;113(7):1807–43, http://dx.doi.org/10.1002/cncr.23648.
16. Lairmore TC, Piersall LD, DeBenedetti MK, Dilley WG, Mutch MG, Whelan AJ, et al. Clinical genetic testing and early surgical intervention in patients with multiple endocrine neoplasia type 1 (MEN 1). Ann Surg. 2004;239(5):637–45; discussion 645–7, http://dx.doi.org/10.1097/01.sla.0000124383.98416.8d.
17. Tonelli F, Fratini G, Nesi G, Tommasi MS, Batignani G, Falchetti A, et al. Pancreatectomy in multiple endocrine neoplasia type 1-related gastrinomas and pancreatic endocrine neoplasias. Ann Surg. 2006;244(1):61–70, http://dx.doi.org/10.1097/01.sla.0000218073.77254.62.
18. Thompson NW. Management of pancreatic endocrine tumors in patients with multiple endocrine neoplasia type 1. Surg Oncol Clin N Am. 1998;7(4):881–91.
19. Norton JA, Jensen RT. Resolved and unresolved controversies in the surgical management of patients with Zollinger-Ellison syndrome. Ann Surg. 2004;240(5):757–73, http://dx.doi.org/10.1097/01.sla.0000143252.02142.3e.
20. Thompson NW. Current concepts in the surgical management of multiple endocrine neoplasia type 1 pancreatic-duodenal disease. Results in the treatment of 40 patients with Zollinger-Ellison syndrome, hypoglycaemia or both. J Intern Med. 1998;243(6):495–500, http://dx.doi.org/10.1046/j.1365-2796.1998.00307.x.
21. Demeure MJ, Klonoff DC, Karam JH, Duh QY, Clark OH. Insulinomas associated with multiple endocrine neoplasia type I: the need for a different surgical approach. Surgery. 1991;110(6):998–1004; discussion 1004–5.
22. Rasbach DA, van Heerden JA, Telander RL, Grant CS, Carney JA. Surgical management of hyperinsulinism in the multiple endocrine neoplasia, type 1 syndrome. Am J Med. 1985;78(2):337–42, http://dx.doi.org/10.1016/0002-9343(85)90446-2.
23. Simon D, Starke A, Goretzki PE, Roeher HD. Reoperative surgery for organic hyperinsulinism: indications and operative strategy. World J Surg. 1998;22(7):666–71, http://dx.doi.org/10.1007/s002689900450.
24. Oberg K, Astrup L, Eriksson B, Falkmer SE, Falkmer UG, Gustafsen J, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine tumours (including bronchopulmonary and thymic neoplasms). Part I – general overview. Acta Oncol. 2004;43(7):617–25, http://dx.doi.org/10.1080/02841860410018575.
25. Oberg K. Diagnostic work-up of gastroenteropancreatic neuroendocrine tumors. Clinics. 2012;67(S1):109–12, http://dx.doi.org/10.6061/clinics/2012(Sup01)18.
26. Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol. 2008;9(1):61–72, http://dx.doi.org/10.1016/S1470-2045(07)70410-2.
27. van Vilsteren FG, Baskin-Bey ES, Nagorney DM, Sanderson SO, Kremers WK, Rosen CB, et al. Liver transplantation for gastroenteropancreatic neuroendocrine cancers: Defining selection criteria to improve survival. Liver Transpl. 2006;12(3):448–56, http://dx.doi.org/10.1002/lt.20702.