Surgical Strategy in the Treatment of Pancreatic Neuroendocrine Tumors

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Summary

Endocrine pancreatic tumors are rare and their surgical treatment is often debated. This review analyzes the management and the different indications in functioning and non-functioning neoplasms. The choice among different procedures is described as well as the role of intra operative ultrasound. Moreover, the different patterns of tumor spread are considered (local, loco-regional and metastatic) along with the indications according to the main controversies relating to cytoreductive surgery, transplantation and multiple endocrine neoplasia type 1 patients.

Introduction

In recent years, new diagnostic and therapeutic procedures have increased the attention given to pancreatic endocrine tumors, but they still remain a rare disease (incidence 4/1,000,000 inhabitants/year) [1].

They are usually characterized by a good prognosis (5-year overall survival of 80%) and by a slow progression, giving a wide range of options for surgical treatment [2]. Moreover, surgery is justified not only for curative purposes but also for palliative purposes.

Even if they belong to the same family, they can be very different as for functional status, tumor size, multiplicity, potential or manifest malignancy and stage of the disease at the time of diagnosis. In 2000, WHO published a new clinicopathological classification which can be useful in better correlating these parameters with the prognosis [3]. However, their heterogeneity makes it hard to define accepted surgical protocol. The matter is further complicated by the length of the natural history. But in the case of radical resection, it is difficult to establish what the true impact of surgical therapy on prognosis actually is.

In the present paper, we will try to point out the more important issues on the surgical strategy in non-functioning and functioning pancreatic endocrine neoplasms.

Surgical Indications in the Case of Unidentified Lesions

The presence of a hormonal syndrome may give rise to a singular problem for surgical strategy, namely, making an early clinical diagnosis, without the presence of an evident lesion at imaging techniques. This is especially true for the two most common functioning pancreatic tumors, such as insulinoma and gastrinoma. Notwithstanding achievements accomplished in the field of imaging techniques, they are not able to evidence the tumor in 10-20% of cases, due to their small size and, in the case of

gastrinomas, due to their possible extra-duodenal pancreatic origin. In this situation, when a team of experts reaches a diagnosis, the surgeon can perform a laparotomy with a good certainty of identifying the tumor. The surgical procedures have to be quite rigorous [4, 5, 6]. After a careful abdominal exploration, the pancreatic gland should be widely exposed using the Kocher maneuver, and dissection of both the superior and the inferior margins of the gland and of the splenic ligament. In this way, the pancreas will become accessible for a bi-digital manual examination and the entire parenchyma can be studied using intra-operative ultrasound with a 10 or a 7.5 MHz probe. Insulinomas appear visually as gray-reddish masses, with a higher consistency in comparison to the surrounding parenchyma. Ultrasound reveals a hypoechogenic aspect. The use of intra-operative ultrasound allows the identification of 88% of insulinomas, 91% of pancreatic gastrinomas and approximately 30% of duodenal gastrinomas [7, 8].

Since gastrinomas may have an extra-duodenal pancreatic localization, the procedure should be completed with a careful exploration of the stomach, the mesenterium, and the entire abdominal and pelvic cavities.

In Zollinger-Ellison syndrome, the surgeon should also perform a duodenal trans-illumination followed by a 3 cm longitudinal duodenal incision. This maneuver allows a complete examination of the entire mucosal surface, including the medial wall. The sensitivity of duodenotomy is indeed higher (100%) in comparison to palpation (61%), and intra-operative ultrasound imaging (26%) associated with trans-illumination (64%) [9]. If properly executed, this protocol is associated with an extremely low percentage of failure (less than 7%) in identifying the tumor [4]. According to Norton *et al.* [10], in the case of gastrinomas, the use of this protocol has increased the frequency of detection from 64 to 92% largely due to the increased attention to duodenal localizations. When, despite such a procedure, the tumor cannot be localized, the literature clearly states the uselessness of a so-called "blind resection" [11, 12]. In consideration of the fact that insulinomas do not have a particular prevalence for any specific localization within the pancreas and their low grade of malignancy (only 10% of cases) [13], a surgeon who fails to identify the lesion during laparotomy, should refrain from pancreatic resection. A postoperative Dopmann test must be carried out in order to localize the disease [14, 15]. When even this latter fails to localize the tumor, close follow-up of the patient is recommended until the lesion is identified. Although data regarding this issue are incomplete, it would seem that a blind resection of the pancreas should be considered only in those cases in which venous sampling allows the localization of the tumor and when medical therapy does not result in satisfactory control of the clinical symptoms [16]. As regards gastrinomas, although these tumors are characterized by a high grade of malignancy (60-90% of cases) [12], a blind resection would appear in any case disproportionate due to both the high variability of localization and, thanks to medical therapy, the current control of disease progression. Proton pump inhibitors have restricted the indication for surgical procedures, such as antrectomy and total gastrectomy, with the aim of controlling clinical symptoms through the removal of the target organ [11, 17].

Radical Resections

After identification, there is no doubt about the surgical indication in all localized tumors. The choice of procedure will depend on the risk of malignancy based on parameters such as type, size and features of the mass. Atypical resection (enucleation or middle pancreatectomy) has the advantage of preserving the pancreatic parenchyma as much as possible, thereby reducing the risk of late exocrine/endocrine insufficiency. However, since in these procedures, a lymphadenectomy is not usually performed, they are not "foolproof" in oncological terms.

Enucleation can usually be performed in those cases where the lesion is single, capsulated, of limited dimensions (less than 4 cm in diameter) and does not involve, or is "sufficiently far" from the main pancreatic duct [18]. When the lesion is in the body and/or nearby the Wirsung duct, a middle pancreatectomy should be the procedure of choice. In these instances, enucleation would be at very high risk for a postoperative fistula. Insulinomas and small non-functioning tumors are the most indicated cases. It has been debated whether or not enucleation is the correct treatment also for gastrinomas which are usually small in size but with a high rate of malignancy. Authors advocating atypical resection report a 10-year survival rate of 94% but with a low disease-free postoperative rate (51%) [4]. This percentage is reported to be close to 90% by authors who routinely perform typical resections [19].

In all other situations, a typical resection (pancreaticoduodenectomy or distal pancreatectomy), in accordance with the site, appears to be the standard procedure [20, 21, 22]. In fact, in the case of malignancy, these resections allow a consensual node dissection as standardized for exocrine tumors.

Extended Resections

When radicality is doubtful or only achievable by the demolition of nearby organs (stomach, colon, kidney, adrenal gland) or by further vascular resection, an intra-operative histological diagnosis is indicated [12, 23, 24, 25, 26]. If the endocrine nature of the tumor is confirmed, an aggressive treatment is justified even if other organs and/or portal-mesenteric vein confluence resection are necessary. The involvement of the superior mesenteric artery and/or the celiac trunk is less frequent [23, 25]. In our experience, the median survival of this group of patients is 65 months, but 66% of them eventually present liver metastases at follow-up.

Radical Resections in Case of Liver Involvement

At diagnosis, about 60% of non-functioning endocrine pancreatic tumors and 50% of gastrinomas are metastatic. Whenever a resection leaves no residual disease, an aggressive approach is proposed in the presence of synchronous or metachronous hepatic metastases [27, 28, 29, 30]. In fact, simultaneous resection of both the primary tumor and all the hepatic metastases (or their subsequent removal) does not seem to be an unfavorable prognostic factor [31, 32]. Unfortunately, at diagnosis, this is feasible in only less than 20% of patients, due to the high percentage of multifocal and bilateral metastases. When this approach is applicable, the 5-year actuarial survival rate is 73%, but recurrence is almost always the rule, with the time to progression proportional to the intrahepatic diffusion [31, 32].

Not Radical Surgical Resections (Debulking)

The appropriate management of patients whose resection would leave macroscopic residual disease (R2) is still being debated. This situation is usually due to the presence of "notable and massive" local infiltration (vessels, organs, retroperitoneum) and/or not completely resectable liver metastases.

Many surgeons have suggested cytoreductive surgery or debulking. What cytoreductive surgery means is an even more controversial matter. It should be remembered that, from an oncological point of view, the debulking must reduce the mass by at least 90%, which is seldom possible. This rationale is based on: 1) the possibility of treating the residual mass with loco-regional therapies; 2) allowing better control of the symptoms due to hypersecretion, whenever present; 3) prolonging survival. Duodenal pancreatic mass debulking has also been suggested as a preventive method against complications

related to local growth of the tumor, such as recurrent pancreatitis, biliary or intestinal occlusion and gastrointestinal bleeding.

In truth, surgical resection does not appear justifiable in all cases of locally incomplete resectable disease. In fact, existing data do not justify a local partial resection of the mass, which would lead to the fragmentation of the tumor in the peritoneal cavity. Moreover, the hypervascularization of these neoplasms implies a high risk of bleeding. Since local relapse is the rule, the eventual palliation of symptoms due to the mass is only temporary. Furthermore, the survival rate of unresected patients with locally advanced disease remains 44% at 5 years [33].

For those patients who complain of biliary and/or gastrointestinal tract occlusion, palliative surgical procedures are indicated. The long-term life expectancy of these patients, whenever endoscopic palliative treatment was preferred, would mean endoprosthesis substitution several times during the course of their lives [12, 34]. For this reason, surgical bypasses would be preferred. In the case of jaundice, even without alimentary disturbances, it might be useful to add a prophylactic gastrointestinal-anastomosis to biliary decompression [35, 36, 37].

The cytoreductive surgery of the hepatic metastases after radical resection of the primary tumor seems to play a limited role in non-functioning or low symptomatic tumors since it does not lead to a significant increase in survival [31, 38]. In non-functioning lesions, when less than 90% of the tumor is resectable and there are no symptoms of loco-regional compression, chemoembolization seems to be the best treatment [31]. Whenever feasible, debulking seems to better control the symptoms in functioning tumors such as malignant insulinomas. In this latter situation, medical treatment leads only to limited relief. On the contrary, for gastrinomas, the availability of an effective medical therapy contraindicates liver cytoreduction.

However, even in the presence of unresectable liver metastases, total resection

of the primary tumor seems to play a role [34]. In fact, resection of the primary tumor might avoid compressive symptoms, optimizing palliation. Moreover, the disease can be "compartmentalized" exclusively to the liver, thus facilitating subsequent appropriate therapies.

As an alternative to surgery, embolization and chemoembolization may be proposed for treatment of residual hepatic disease [38, 39, 40, 41, 42, 43, 44]. To tie off the hepatic artery alone is not enough since collateral circulation quickly appears [45]. At present, the first results with dia-termo-ablation are beginning to emerge [46]. Limited experience still makes this technique experimental.

Liver transplantation should be also considered as experimental. Authors agree in selecting patients under 60 years of age, with non-resectable hepatic metastases, no extra-hepatic abdominal diffusion and when the most standard therapeutic options have failed [47, 48, 49]. Patients selected following the above indications show a global survival rate of 36% at 5 years with 17% of survivors completely disease-free [49]. Indications based on rapid tumor growth seem to be more disputable [47, 48].

Cholecystectomy

Somatostatin analogue therapy is usually the treatment of choice for those patients suffering from non-resectable disease. This treatment is associated with a risk of developing gallstones and gallstone sludge in up to 50% of cases. Moreover, liver chemoembolization presents a high risk of cholecystitis. For all these reasons, cholecystectomy should be performed whenever a surgical procedure is required [50].

Surgical Indications in multiple endocrine neoplasia type 1 (MEN-1)

Surgeons should bear in mind that the association of endocrine pancreatic tumors

with hereditary diseases, such as MEN-1, may change surgical strategy.

Up to 75% of patients affected by MEN-1 develop synchronous or metachronous islet cell pancreatic or duodenal tumors: gastrinomas (60%), insulinomas and non-functional tumors (20% each) [51]. The operative management must be individualized taking into account their tendency towards multicentricity and the high recurrence rates. The timing of surgery is still under debate. Some authors suggest surgery only for masses larger than 2-3 cm in size due to their high metastatic potential [52, 53]. Others feel that aggressive surgery is indicated in the presence of any biochemical positive marker [54]. The aim of surgery is to achieve complete tumor resection preserving the pancreatic function and minimizing the morbidity. Due to the high rate of multicentricity, intraoperative ultrasound is mandatory. The frequent multiplicity of the lesions often results in a subtotal distal pancreatectomy with enucleation of those tumors located in the head or in the duodenum [55]. Total pancreatectomy, though effective as "organ disease eradication" and as prevention of relapses, is not generally recommended. It should be taken into consideration only in those cases in which lesions are multicentric and the familial history evidences high mortality rates for the disease.

Keywords Neuroendocrine Tumors; Pancreatic Neoplasms; Surgical Procedures, Operative

Abbreviations MEN-1: multiple endocrine neoplasia type 1

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References

1. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003; 97:934-59. [PMID 12569593]

2. Eriksson B, Arnberg H, Lindgren PG, Lorelius LE, Magnusson A, Lundqvist G, et al. Neuroendocrine pancreatic tumours: clinical presentation, biochemical and histopathological findings in 84 patients. J Intern Med 1990; 228:103-13. [PMID 2168468]

3. Solcia E, Kloppel G, Sobin L. Histological typing of the endocrine tumours. Berlin Heidelberg: Springer-Verlag; 2000.

4. Norton JA, Fraker DL, Alexander HR, Venzon DJ, Doppman JL, Serrano J, et al. Surgery to cure the Zollinger-Ellison syndrome. N Engl J Med 1999; 341:635-44. [PMID 10460814]

5. Prinz RA. Localization of gastrinomas. Int J Pancreatol 1996; 19:79-91. [PMID 8723550]

6. Rothmund M. Localization of endocrine pancreatic tumours. Br J Surg 1994; 81:164-6. [PMID 8156325]

7. Norton JA, Cromack DT, Shawker TH, Doppman JL, Comi R, Gorden P, et al. Intraoperative ultrasonographic localization of islet cell tumors. A prospective comparison to palpation. Ann Surg 1988; 207:160-8. [PMID 2829761]

8. Klotter HJ, Ruckert K, Kummerle F, Rothmund M. The use of intraoperative sonography in endocrine tumors of the pancreas. World J Surg 1987; 11:635-41. [PMID 2823490]

9. Sugg SL, Norton JA, Fraker DL, Metz DC, Pisegna JR, Fishbeyn V, et al. A prospective study of intraoperative methods to diagnose and resect duodenal gastrinomas. Ann Surg 1993; 218:138-44. [PMID 8342993]

10. Norton JA, Doppman JL, Jensen RT. Curative resection in Zollinger-Ellison syndrome: results of a ten year prospective study. Ann Surg 1992; 215:8-18. [PMID 1531004]

11. Norton JA. Neuroendocrine tumors of the pancreas and duodenum. Curr Probl Surg 1994; 31:77-156. [PMID 7904550]

12. Delcore R, Friesen SR. Gastrointestinal neuroendocrine tumors. J Am Coll Surg 1994; 178:187-211. [PMID 8173736]

13. Vinik AI, Moattari AR. Treatment of endocrine tumors of the pancreas. Endocrinol Metab Clin North Am 1989; 18:483-518. [PMID 2663483]

14. Peplinski GR, Skinner MA, Norton JA. Insulinoma and nesidioblastosis. In: Howard J, Idezuki Y, Ihse I, Prinz R, eds. Surgical Disease of the Pancreas, 3rd Ed. Baltimore, MD, USA: Williams and Wilkins, 1998:717-32. [ISBN 0-683-18019-3]

15. Van Heerden J. The surgical treatment of insulinomas. In: Beger HG, Warshaw Al, Buchler MW, Carr-Locke DL, Neoptolemos JP, C RussellC, eds. The Pancreas. Oxford, UK: Blackwell Science, 1998:1203-12. [ISBN 865424209]

16. Miller DL. Endocrine angiography and venous sampling. Radiol Clin North Am 1993; 31:1051-67. [PMID 8362055]

17. Brennan MF, Jensen RT, Wesley RA, Doppman JL, McCarthy DM. The role of surgery in patients with Zollinger-Ellison syndrome (ZES) managed medically. Ann Surg 1982; 196:239-45. [PMID 7114932]

18. Park BJ, Alexander HR, Libutti SK, Huang J, Royalty D, Skarulis MC, et al. Operative management of islet-cell tumors arising in the head of the pancreas. Surgery 1998; 124:1056-61. [PMID 9854583]

19. Stadil F. Treatment of gastrinomas with pancreaticoduodenectomy. In: Jensen RT, Mignon M, eds. Endocrine Tumors of the Pancreas: Recent Advances in Research and Management. Basel, Switzerland: Karger, 1994:333-41.

20. Delcore R, Friesen SR. Role of pancreatoduodenectomy in the management of primary duodenal wall gastrinomas in patients with Zollinger-Ellison syndrome. Surgery 1992; 112:1016-22. [PMID 1360709]

21. Phan GQ, Yeo CJ, Hruban RH, Lillemoe KD, Pitt HA, Cameron JL. Surgical experience with pancreatic and peripancreatic neuroendocrine tumors: review of 125 patients. J Gastrointest Surg 1998; 2:472-82. [PMID 9843608]

22. Jordan PH Jr. A personal experience with pancreatic and duodenal neuroendocrine tumors. J Am Coll Surg 1999; 189:470-82. [PMID 10549736]

23. Dial PF, Braasch JW, Rossi RL, Lee AK, Jin GL. Management of nonfunctioning islet cell tumors of the pancreas. Surg Clin North Am 1985; 65:291-9. [PMID 2990058]

24. Madura JA, Cummings OW, Wiebke EA, Broadie TA, Goulet RL Jr, Howard TJ. Nonfunctioning islet cell tumors of the pancreas: a difficult diagnosis but one worth the effort. Am Surg 1997; 63:573-7. [PMID 9202529]

25. Bartsch DK, Schilling T, Ramaswamy A, Gerdes B, Celik I, Wagner HJ, et al. Management of nonfunctioning islet cell carcinomas. World J Surg 2000; 24:1418-24. [PMID 11038216]

26. Matthews BD, Heniford BT, Reardon PR, Brunicardi FC, Greene FL. Surgical experience with nonfunctioning neuroendocrine tumors of the pancreas. Am Surg 2000; 66:1116-22. [PMID 11149582]

27. Norton JA, Sugarbaker PH, Doppman JL, Wesley RA, Maton PN, Gardner JD, Jensen RT. Aggressive resection of metastatic disease in selected patients with malignant gastrinoma. Ann Surg 1986; 203:352-9. [PMID 2938550]

28. McEntee GP, Nagorney DM, Kvols LK, Moertel CG, Grant CS. Cytoreductive hepatic surgery for neuroendocrine tumors. Surgery 1990; 108:1091-6. [PMID 1701060]

29. Danforth DN Jr, Gorden P, Brennan MF. Metastatic insulin-secreting carcinoma of the pancreas: clinical course and the role of surgery. Surgery 1984; 96:1027-37. [PMID 6095477]

30. Carty SE, Jensen RT, Norton JA. Prospective study of aggressive resection of metastatic pancreatic endocrine tumors. Surgery 1992; 112:1024-31. [PMID 1455305]

31. Chamberlain RS, Canes D, Brown KT, Saltz L, Jarnagin W, Fong Y, Blumgart LH. Hepatic neuroendocrine metastases: does intervention alter outcomes? J Am Coll Surg 2000; 190:432-45. [PMID 10757381]

32. Chen H, Hardacre JM, Uzar A, Cameron JL, Choti MA. Isolated liver metastases from neuroendocrine tumors: does resection prolong survival? J Am Coll Surg 1998; 187:88-92. [PMID 9660030]

33. Evans DB, Skibber JM, Lee JE, Cleary KR, Ajani JA, Gagel RF, et al. Nonfunctioning islet cell carcinoma of the pancreas. Surgery 1993; 114:1175-81. [PMID 7903005]

34. Pederzoli P, Falconi M, Bonora A, Salvia R, Sartori N, Contro C, et al. Cytoreductive surgery in advanced endocrine tumours of the pancreas. Ital J Gastroenterol Hepatol 1999; 31(Suppl 2):S207-12. [PMID 10604132]

35. Speer AG, Cotton PB, Russell RC, Mason RR, Hatfield AR, Leung JW, et al. Randomised trial of endoscopic versus percutaneous stent insertion in malignant obstructive jaundice. Lancet 1987; 2:57-62. [PMID 2439854]

36. Andersen JR, Sorensen SM, Kruse A, Rokkjaer M, Matzen P. Randomised trial of endoscopic endoprosthesis versus operative bypass in malignant obstructive jaundice. Gut 1989; 30:1132-5. [PMID 2475392]

37. Welvaart K. Operative bypass for incurable cancer of the head of the pancreas. Eur J Surg Oncol 1992; 18:353-6. [PMID 1381687]

38. Falconi M, Bassi C, Bonora A, Sartori N, Procacci C, Talamini G, et al. Role of chemoembolization in synchronous liver metastases from pancreatic endocrine tumours. Dig Surg 1999; 16:32-8. [PMID 99136138]

39. Mavligit GM, Pollock RE, Evans HL, Wallace S. Durable hepatic tumor regression after arterial chemoembolization-infusion in patients with islet cell carcinoma of the pancreas metastatic to the liver. Cancer 1993; 72:375-80. [PMID 93306579]

40. Nesovic M, Ciric J, Radojkovic S, Zarkovic M, Durovic M. Improvement of metastatic endocrine tumors of the pancreas by hepatic artery chemoembolization. J Endocrinol Invest 1992; 15:543-7. [PMID 93077918]

41. Marlink RG, Lokich JJ, Robins JR, Clouse ME. Hepatic arterial embolization for metastatic hormone-secreting tumors. Technique, effectiveness, and complications. Cancer 1990; 65:2227-32. [PMID 90268389]

42. Ruszniewski P, Rougier P, Roche A, Legmann P, Sibert A, Hochlaf S, et al. Hepatic arterial chemoembolization in patients with liver metastases of endocrine tumors. A prospective phase II study in 24 patients. Cancer 1993; 71:2624-30. [PMID 93201492]

43. Clouse ME, Perry L, Stuart K, Stokes KR. Hepatic arterial chemoembolization for metastatic neuroendocrine tumors. Digestion 1994; 55(Suppl 3):92-7. [PMID 95212792]

44. Eriksson BK, Larsson EG, Skogseid BM, Lofberg AM, Lorelius LE, Oberg KE. Liver embolizations of patients with malignant neuroendocrine gastrointestinal tumors. Cancer 1998; 83:2293-301. [PMID 99054263]

45. Wiedenmann B, Jensen RT, Mignon M, Modlin CI, Skogseid B, Doherty G, et al. Preoperative diagnosis and surgical management of neuroendocrine gastroenteropancreatic tumors: general recommendations by a consensus workshop. World J Surg 1998; 22:309-18. [PMID 98155529]

46. Oberg K. State of the art and future prospects in the management of neuroendocrine tumors. Q J Nucl Med 2000; 44:3-12. [PMID 20387969]

47. Lang H, Oldhafer KJ, Weimann A, Schlitt HJ, Scheumann GF, Flemming P, et al. Liver transplantation for metastatic neuroendocrine tumors. Ann Surg 1997; 225:347-54. [PMID 9114792]

48. Frilling A, Rogiers X, Malago M, Liedke O, Kaun M, Broelsch CE. Liver transplantation in patients with liver metastases of neuroendocrine tumors. Transplant Proc 1998; 30:3298-300. [PMID 99055837]

49. Le Treut YP, Delpero JR, Dousset B, Cherqui D, Segol P, Mantion G, et al. Results of liver transplantation in the treatment of metastatic neuroendocrine tumors. A 31-case French multicentric report. Ann Surg 1997; 225:355-64. [PMID 9114793]

50. Trendle MC, Moertel CG, Kvols LK. Incidence and morbidity of cholelithiasis in patients receiving chronic octreotide for metastatic carcinoid and malignant islet cell tumors. Cancer 1997; 79:830-4. [PMID 9024721]

51. Jensen RT. Pancreatic endocrine tumors: recent advances. Ann Oncol 1999; 10(Suppl 4):170-6. [PMID 99365868]

52. Weber HC, Venzon DJ, Lin JT, Fishbein VA, Orbuch M, Strader DB, et al. Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome: a prospective long-term study. Gastroenterology 1995; 108:1637-49. [PMID 7768367]

53. Mignon M, Cadiot G. Diagnostic and therapeutic criteria in patients with Zollinger-Ellison syndrome and multiple endocrine neoplasia type 1. J Intern Med 1998; 243:489-94. [PMID 9681847]

54. Skogseid B, Oberg K, Eriksson B, Juhlin C, Granberg D, Akerstrom G, et al. Surgery for asymptomatic pancreatic lesion in multiple endocrine neoplasia type I. World J Surg 1996; 20:872-6. [PMID 8678965]

55. 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; 243:495-500. [PMID 9681848]