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Contemporary surgical management of the Zollinger-Ellison syndrome in multiple endocrine neoplasia type 1



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About 30% of patients with MEN1 develop a Zollinger-Ellison syndrome. Meanwhile it is well established that the causative gastrinomas are almost exclusively localized in the duodenum and not in the pancreas, MEN1 gastrinomas occur multicentric and are associated with hyperplastic gastrin cell lesions and tiny gastrin-producing micro tumors in contrast to sporadic duodenal gastrinomas. Regardless of the high prevalence of early lymphatic metastases, the survival is generally good with an aggressive course of disease in only about 20% of patients. Symptoms can be controlled medically. The indication, timing, type, and extent of surgery are highly controversial and are discussed in detail in this article by a thorough and critical review of literature. More radical procedures, like partial pancreaticoduodenectomy, are weighed against less aggressive local excision of gastrinomas and the pros and cons of both approaches are discussed in terms of long-term morbidity, biochemical cure, and survival.

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Background

Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant inherited tumor syndrome caused by germline mutations of the *Menin* gene on chromosome 11q13 [1]. The syndrome is classically characterized by the development of adenomas of the anterior pituitary gland, parathyroid gland hyperplasia, and pancreatic neuroendocrine neoplasms (pNEN) among tumors of numerous other primary locations [2]. The disease penetrance approximates 100% [3,4]. During the past decade, several groups extensively studied the disease, which led to a clearer understanding of the clinical course of the syndrome and its treatment options. This knowledge resulted in the development of international practice guidelines [5–7]. It has to be stated, however, that these guidelines are based on a low level of evidence regarding pancreatic neuroendocrine neoplasms (pNEN), since only retrospective or prospective observational studies exist, given the rarity of disease.

Regular screening at expert centers is recommended for all patients with MEN1. This may lead to the early detection and treatment of pNENs and result in prolonged survival. Besides the rare, but very aggressive thymic NEN, pNEN are the most common cause of disease-related death of MEN1 patients [4,8]. According to recent studies, at least 80% of patients with the MEN1 syndrome develop pNEN, most of which are non-functioning and do not require treatment [9–11]. However, pNEN larger than 20 mm or with a rapid growth are at risk for the development of metastatic disease [12,13]. Functioning pNEN cause specific clinical syndromes by hypersecretion of specific hormones such as insulin or gastrin and require treatment. A recent retrospective French cohort study showed that Zollinger-Ellison-related tumors, pNENs over 2 cm, and age over 40 years were independently associated with an increased risk of metastases [13].

Approximately 30% of patients with MEN1-associated pNEN are diagnosed with the Zollinger-Ellison-Syndrome. It has to be emphasized that patients with MEN1-ZES also have a high prevalence of concomitant non-functioning pNENs. Whereas NF-pNENs occur frequently within the second decade of life, gastrinomas are exceptional before the age of 20 years [10,11]. In contrast to the perception of numerous older studies, it is nowadays well established, that gastrinomas - unlike the other functioning as well as the non-functioning pNEN - are almost exclusively located in the duodenum and not in the pancreas [14–19]. Pathological studies also showed, that MEN1-associated duodenal gastrinomas [19], are often multiple and preceded by gastrin cell proliferation [20]. Therefore, the duodenum - and not the pancreas - is the target organ of any surgical therapy of MEN1-ZES. This knowledge was not applied in the vast majority of studies before 2010. In these studies, visible pancreatic tumors in patients with MEN1-ZES were frequently defined as gastrinomas, although those were most likely only concomitant non-functioning pNEN ([8,21–24]. Even in recently published studies with long-term follow-up it was not possible to clearly define the localization of gastrin secretion in a significant number of patients, either by immunohistochemistry of the resected pNEN and/or biochemical cure after resection [13].

Unlike pancreatic NEN, which usually do not metastasize up to a size of 20 mm [12], about 70%–80% of gastrinomas are metastatic to regional lymph nodes at the time of diagnosis, even though the duodenal wall gastrinomas are usually as small as 3–5 mm in diameter [15–18,25]. MEN1-ZES lymph node metastases do not seem to negatively affect overall survival [13,18]. Approximately every fourth patient with MEN1-ZES, however, shows an aggressive course of disease with the development of distant metastases and premature death [8,17,23,24]. Unfortunately, there is yet no reliable marker or parameter that indicates an aggressive course of disease in MEN1-ZES. Recently it has been suggested that loss of interaction with the CHES1 or JunD domains of MENIN might indicate aggressive pNENs, including gastrinoma in MEN1, which still awaits confirmation in large scale studies [26,27].

Diagnosis of the Zollinger-Ellison syndrome

The Zollinger-Ellison syndrome (ZES) is defined by hypergastrinemia in the prevalence of acid in the stomach ($\text{pH} < 4$). The correct diagnosis of ZES has become more difficult, because of a widespread use of unreliable gastrin assays, the limited availability of secretin, the frequent use of proton pump inhibitors (PPI), and synchronous primary hyperparathyroidism [6,28]. Since both, hypercalcemia and PPI therapy, increase the serum gastrin level and lead to a false positive secretin stimulation test,

successful treatment of hyperparathyroidism and PPI abstinence over at least 48 h are required before ZES can be correctly diagnosed. Somatostatin receptor-PET/CT is generally not recommended for regular screening of MEN1 patients [5,29]. In MEN1 patients with ZES, however, it should be performed in combination with endoscopic ultrasonography before surgical treatment to guide the surgical strategy by visualization of duodenal gastrinomas, concomitant pNENs and metastases [29,30].

Indication for and timing of surgery

The management of MEN1-gastrinoma, either medical treatment with PPI or surgery, is highly controversial, especially since symptoms of MEN1-ZES can be well controlled medically. Previous expert guidelines suggested medical management using PPI for the majority of patients, since the course of disease is rather mild and MEN1-ZES is considered a surgically non-curable disease [5]. This recommendation is based on retrospective data demonstrating a 15-years survival of up to 90% in MEN1 patients with ZES and no imageable tumor, and even a 10-years survival of 54% in patients with diffuse distant metastases at the time of diagnosis [17]. Somatostatin analogue treatment has been applied to patients with sporadic ZES, including very few with MEN1-ZES and showed an antisecretory effect and also an antitumor effect [31–33]. Overall, these reports included less than 10 patients with MEN1-ZES with a maximum follow up of 7 years [33] and its value in these patients remains uncertain.

Despite the overall good survival of patients with MEN1-ZES, one has to take into account that the typical MEN1-ZES patient is around 35 years at the time of diagnosis. One could argue that 15–20 years of survival resulting in premature death before the age of 60 years in a substantial number of patients [13] cannot be the true goal of modern health care. This point has to be considered seriously, since several groups have demonstrated, that complete resection of MEN1 gastrinomas prevents the development of distant metastases in 90–100% of patients and prolongs survival compared to non-surgery or R2 resection [15,16,18,22,23,34–38]. Moreover, some small-scale studies have shown that a significant proportion of patients with MEN1-ZES were cured in the long-term, if the target organ duodenum was removed [15,18,35,36]. Furthermore, long standing excess of gastrin, caused by gastrinomas, intake of proton pump inhibitors, or hyperparathyroidism, can lead to hyperplasia of gastric enterochromaffin-like cells and a subsequent growth of neuroendocrine gastric neoplasms, which might be prevented by resection of gastrinomas [39,40].

The optimal time point of any surgical approach is also controversial. Most groups recommend an operative approach only, if an imageable duodenopancreatic tumor reaches 2–3 cm in size, since the risk for liver metastases then increases significantly [8,17,23,41]. This policy is mainly based on an older study of Weber et al. from the NIH group published in 1995 [23]. They demonstrated in a retrospective study on 118 MEN1-ZES patients with pNENs visualized by imaging, that the prevalence of liver metastases was 4% in patients with pNENs <1 cm, 28% in patients with pNENs between 1 and 3 cm and 61% in patients with pNENs >3 cm in size, respectively. Based on the current knowledge, these pNEN, however, were most likely concomitant non-functioning pNEN, especially since the study does not report on immunohistochemical staining of gastrin in the tumor and the metastases. The vast majority of the patients in this and in numerous other older studies [22,23] would have had duodenal gastrinomas and the imaged “pancreatic gastrinomas”, which were not proven based on histopathology including immunohistochemistry for gastrin expression, were most likely non-functioning pNENs. Therefore, the correct interpretation of such imageable pancreatic tumors (≥ 2 cm) in MEN1-ZES has to be related to NF-pNENs and not to gastrinoma. Nevertheless, the presence of an imageable pancreatic lesion ≥ 2 cm in MEN1-ZES might be a useful surrogate parameter to indicate surgery.

More recently, a few groups could demonstrate in small cases series that partial pancreaticoduodenectomy (PPD) as initial procedure at the time of biochemical evidence of ZES, even without positive imaging studies, resulted in a high rate of biochemical cure ranging from 77% to 92% without mortality after median 3–7 years [15,18,35,36,42] (Table 2).

Concepts of primary surgery

The surgical strategy is another controversial issue in MEN1-ZES. There are no randomized controlled nor controlled comparative studies that evaluated the optimal surgical procedure for MEN1-

Table 1

Results of duodenum preserving operations for MEN1 associated ZES.

author	year of publication	n	follow-up (median, months)	biochemical persistence or recurrence	distant metastases during follow up
Norton [17]	2001	48	122	46 (96%)	3 (6%)
Thompson [22]	1998	40	126	27 (62%)	1 (3%)
Cadiot [8]	1999	36	95	35 (97%)	5 (13%)
Dickson [36]	2011	11	44	8 (73%)	1 (9%)
McFarlane [45]	1995	10	18	10 (100%)	0
Lopez [18]	2013	9	136	6 (67%)	0

Only studies providing information on the listed variables were included in the table.

Table 2

Results of (partial) pancreaticoduodenectomy for MEN1 associated ZES.

author	year of publication	n	follow-up (range, months)	biochemical persistence or recurrence	distant metastases during follow up
Tonelli [35]	2006	13	6–36	3 (23%)	1 (9%)
Lopez [18]	2013	13	6–132	1 (9%)	0
Dickson [36]	2011	3	12–48	0	0
Stadil [42]	1993	3	60–132	0	0
Imamura [15]	1995	3	48–221	0	0

Only studies providing information on the listed variables were included in the table.

ZES with regards to biochemical cure, complications, and recurrence. Independent of the surgical procedure the reported morbidity rates range from 30% to 40% and the reported perioperative mortality is below 2%, which is in the lower range of those reported for pancreatic surgery [8,15,19,22–24,41]. The cure rates after surgery range from 0% to 100% depending on the surgical procedure (Tables 1 and 2). Most studies reported success rates of surgical therapy without providing either postoperative normal fasting gastrin levels or a normal secretin test to prove biochemical cure. Furthermore, the follow-up periods after surgery are often rather short to determine the true long-term outcome.

Thus, not only the indication and timing of surgery for MEN1-ZES is controversial, but also the extent of surgery, especially with regards to pancreatic resections. It is now, however, consensus that any operation for MEN1-ZES should include an exploration of the duodenum via duodenotomy or even resection of the duodenum with a systematic peripancreatic lymphadenectomy, including the gastrinoma triangle, to provide a chance of cure [5,6,15,43,44]. Most experts also agree that the very rare pancreatic gastrinomas should be either enucleated, if technically feasible, or removed by a formal pancreatic resection, both combined with a systematic lymphadenectomy [44].

Potential operations for duodenal MEN1-ZES include duodenotomy with local excision of duodenal wall tumors (with or without left pancreatectomy), and duodenectomy (pancreas preserving or as part of partial pancreaticoduodenectomy), both in combination with a systematic lymphadenectomy [5,15,18,22,43,44]. The most common proposed operation for duodenal gastrinomas includes duodenotomy with excision of duodenal wall tumors, enucleation of any tumors of the pancreatic head, lymphadenectomy of peripancreatic nodes, along the celiac trunk and the hepatoduodenal ligament with (Thompson-procedure [22]) or without distal pancreatectomy [5,15,18,22,43,44]. There are no controlled comparative studies evaluating these two procedures and thus there is only weak data to prefer one procedure over the other. Based on retrospective cohort studies there seems to be no difference regarding the cure rate and the prevention of liver metastases [8,17,18,22,36,45] (Table 1). Although neither procedure provides satisfactory biochemical cure rates with only up to 30% of patients with a negative secretin test after 5 years, liver metastases can be prevented in over 95% of patients in the long term [17,18,22,35,36,43]. The indication for a prophylactic distal pancreatectomy, however, must be critically evaluated, since it harbors a significant risk for postoperative pancreoprivic diabetes mellitus (around 30%) and for completion pancreatectomy (up to 16%) during long-term

follow-up [46,47]. With regard to the quality of life and the preservation of pancreatic function the formerly proposed “prophylactic” distal pancreatic resection [48,49] in MEN1-ZES is nowadays highly questionable.

Previously, partial pancreaticoduodenectomy (PPD) has been proposed as first-line procedure for MEN1 associated ZES [15,18,35,36]. Advocates of this approach argue, that only the removal of the target organ in this inherited disease might provide a chance of cure, especially since the often multiple duodenal wall gastrinomas are preceded by ubiquitous duodenal gastrin cell proliferation [19,20] (Fig. 1). It is a question of time, that leaving any duodenal mucosa in place will result in gastrinoma recurrence. Furthermore, peripancreatic and periduodenal lymph node dissection to clear the gastrinoma triangle can be performed more radically compared to duodenum preserving procedures. The resection of concomitant pNEN of the pancreatic head and neck at risk for metastasis pose another argument for PPD. Compared to any duodenum sparing procedures, high biochemical cure rates of 77%–100% have been reported for PPD as primary surgical approach for MEN1-ZES in a few small case series [15,18,35,36,42]. Thus, one might hypothesize, that in contrast to the common believe, localized MEN1-ZES might be surgically curable by an adequate operation at the right time.

On the other hand, there are several arguments against a PPD to treat MEN1-ZES. Despite a greater chance of biochemical cure, this procedure is potentially associated with an increased risk for perioperative complications, long term morbidity and loss of quality of life. In a small retrospective series of 27 MEN1-ZES patients, however, the rate of perioperative complications did not significantly differ between PPD and duodenum preserving procedures (31% vs. 56%), and reoperations were more frequent after duodenum preserving initial surgery (33% vs. 0%, $p = 0.054$) [18]. In another study, the quality of life of 50 patients with MEN1 who underwent duodenopancreatic resections was independent from the performed procedure, either PPD or non-PD resections [50]. Another argument against PPD is the risk of completion pancreatectomy becoming necessary, if new pNENs develop in the pancreatic remnant during the course of disease. As long as the long-term morbidity and influence on the quality of life has not been evaluated in controlled prospective studies, it has to be taken into account that less aggressive operations than PPD resections are associated with excellent long-term survival in MEN1-ZES [13,24].

Imamura et al. recently described the pancreas preserving total duodenectomy (PPTD) as an alternative surgical procedure for duodenal MEN1-ZES [15,51]. Five of 7 patients who underwent this procedure were biochemically cured after 2–6 years. The authors stated that PPTD is a less invasive procedure than PD with no complications in their series. However, they also noted, that dissection of

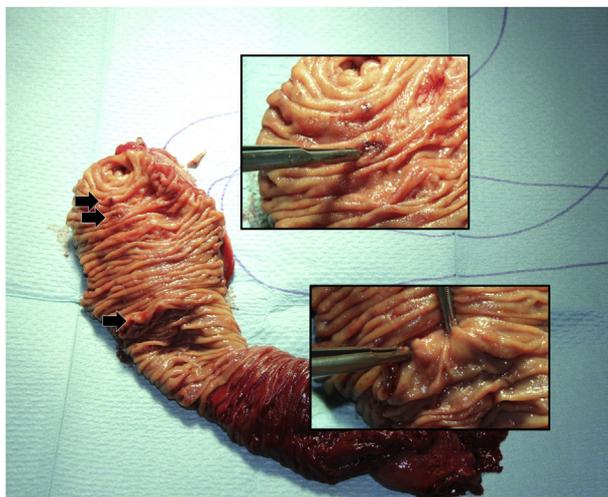


Fig. 1. Specimen of partial pancreaticoduodenectomy with multiple small gastrinomas in the duodenal wall (arrows/instrument tip).

regional lymph nodes may be not as complete by PPTD compared to PPD. This might be the reason for the fact, that 2 of their 7 patients developed ZES recurrence due to liver or distant lymph node metastases within 3 years postoperatively. Moreover, the procedure is technically more demanding than PPD and not well accepted in the surgical community for the treatment of MEN1-ZES to date, considering the very few reports in the literature [15,52,53]. Based on these data the value of the PPTD for the treatment MEN1-ZES can yet not be determined.

The vast majority of experts agree that total pancreaticoduodenectomy as initial procedure for MEN1-ZES should be avoided whenever possible, since the resulting brittle diabetes reduces the quality of life and it is associated with serious morbidity during long-term survival (Vienna MEN1 consensus guidelines, manuscript in preparation). Thus, this procedure should be restricted to rare conditions, such as malignant ZES with multiple large pNENs throughout the whole pancreas.

Role of laparoscopic/robotic surgery in MEN1-ZES

Laparoscopic resection of pNENs, especially insulinomas and non-functioning pNENs, is being increasingly used with good success [54–56]. Although there are reports on the laparoscopic excisions of duodenal NENs via duodenotomy [57] or laparoscopic/robotic PPD-resections [58], there are no published experiences with these techniques in MEN1-ZES. Thus, it is highly questionable, whether laparoscopic duodenotomy allows the intraoperative identification and resection of all duodenal wall gastrinomas in MEN1-ZES. Although laparoscopic or robotic PPD-resections might be feasible and safe [58], they are technically demanding and it has yet to be proven in prospective randomized trials that the postoperative morbidity and mortality rates are at least equal to open surgery. This is of outmost importance, since the potential morbidity and mortality is one major argument against PPD-resections in patients with MEN1-ZES, who are usually young and have a very soft pancreas. For these reasons to date a laparoscopic or robotic approach cannot be recommended for MEN1-ZES.

Role of endoscopic resection of duodenal gastrinomas in MEN1-ZES

Successful endoscopic removal of sporadic duodenal gastrinomas using snare polypectomy or using endoscopic band ligation has been described [59]. However, there are a number of reservations with regard to this approach in MEN1-ZES [60]. First, at least 80% of MEN1-gastrinomas will have lymph node metastases that cannot be approached. Second, most MEN1-gastrinomas occur multiple and sometimes grow invasive beyond the submucosa making the identification as well as the endoscopic removal difficult. Finally, frequent concomitant large pNENs cannot be approached. For these reasons, endoscopic removal of duodenal MEN1-gastrinomas cannot be recommended by the authors.

Acid reducing surgery

The role of simultaneous parietal cell vagotomy with the resection of the primary lesion is a controversial matter of debate. With use of PPIs acid-reducing surgical procedures are rarely indicated. However, despite a generally good safety profile, data on potential adverse effects of long-term use of proton pump inhibitors has recently emerged [61]. Also in consideration of financial aspects vagotomy for MEN1-ZES may be continued. One retrospective study reported, that about 30% of patients with MEN1-ZES did not require antacid medication after vagotomy [62], but in the absence of newer data, this procedure cannot generally be recommended as part of the treatment of MEN1 associated ZES.

Surgical reexploration in MEN1-ZES

At present the indications for surgical reexploration, the type of operation, including completion pancreatectomy, are largely undefined in MEN1-ZES [44] since only few retrospective studies with 2–12 patients dealt with this problem [46,47,63–65]. The indication for reexploration was a biochemically proven recurrence of ZES in combination with imageable disease (e.g. CT/MRI or SRS). The operations included re-duodenotomy with lymphadenectomy, resection of lymph node or liver metastases, PPD-resection or completion pancreatectomy. In these series patients with MEN1-ZES who

underwent reoperations ended up with total pancreatectomy in up to 50%. Although all studies concluded, that reoperations are safe and do not cause a higher rate of complications than initial operations, none of the overall 15 patients with recurrent ZES and long follow up were biochemically cured after the reoperation in the long term [47,65]. Based on the very limited data, it is recommended that the indication for a reexploration in MEN1-ZES should be considered with caution, especially since the symptoms can be well controlled with medical treatment and the long-term survival without distant metastases is excellent. The surgical procedure has to be individualized according to preoperative findings, previous duodenopancreatic resections, patient's history (e.g. age, pre-existing insulin-dependent diabetes), and patient's preference. A completion pancreatectomy should be avoided, if somehow technically possible.

Role of surgery in advanced MEN1-ZES

The most important determinant of survival in patients with MEN1-ZES is the presence or development of hepatic metastases [8,23,41,66]. The extent of liver metastases in ZES seems to be important, since the survival differed significantly between patients with single lobe or less than 5 metastases and patients with diffuse liver metastases [41,66]. Unfortunately, more than 80% of patients have diffuse metastases which are not limited to a small number or one hepatic lobe [41,44]. In various retrospective studies that also included patients with MEN1-ZES, surgery has resulted in cure in a few patients, and 5 years survival rates around 70% were reported after resection of liver metastases [67], but this advantageous survival is likely due to a selection bias of patients with resectable metastatic burden, and there are no controlled trials evaluating cytoreductive surgery in patients with advanced MEN1-ZES. Furthermore, in a recent large retrospective analysis of MEN1 associated metastatic duodenal and pancreatic NETs, the impact of liver metastases on survival was much lower in patients with ZES (hazard ratio 2.08) compared to those without ZES (hazard ratio 12.37) [13]. Unlike for patients with advanced functioning NETs other than gastrinoma, the aim of cytoreductive surgery for patients with ZES should be prolongation of survival and not symptom control.

At present, there are insufficient data for MEN1-ZES to unequivocally determine in which patient cytoreductive surgery of liver metastases should be performed. However, according to most studies, resection of liver metastases can be performed with a low rate of complications and morbidity [67]. It can be postulated that in patients with advanced MEN1-ZES disease confined to the liver, surgery can be considered, if at least 90% of identifiable tumor burden can be safely removed (Vienna MEN1 consensus conference 2017). In the light of various non-operative treatment options such as somatostatin analogues, chemotherapy, TACE and PRRT a balanced approach should be discussed in a multidisciplinary expert team and finally with the patient.

Summary

The target organ of MEN1-ZES is the duodenum and not the pancreas. There is no consensus on the indication and the timing of surgery for MEN1-ZES, since there is yet no proven parameter that indicates an aggressive course of disease and long-term survival is excellent in about 75% of patients. An imageable pNEN ≥ 2 cm, although most likely non-functioning, seems to be a good surrogate parameter to indicate surgery in order to prevent distant metastatic pNEN disease. However, the higher chance of cure when performing a PPD resection at the time of biochemical ZES evidence, even without positive imaging, should be discussed with the patient with regard to benefits and risks. There is also no consensus regarding the type of operation for MEN1-ZES. Any operation for MEN1-ZES should include an exploration of the duodenum via duodenotomy or even resection of the duodenum, both combined with a systematic lymphadenectomy, to provide a chance of cure and to reduce the risk of distant metastatic ZES disease. The surgical procedure should be individualized according to preoperative findings, patient's history (e.g. age, pre-existing insulin-dependent diabetes), and patient's preference. Duodenopancreatic resections for MEN1-ZES should be performed by experienced endocrine surgeons. A future goal would be the identification of a parameter or marker that predict an aggressive course of disease to guide the decision regarding the timing and type of surgery.

Practice Points

- The target organ of MEN1-ZES is the duodenum and not the pancreas.
- There is no consensus on either the indication or the timing of surgery in MEN1-ZES, since no parameter has been shown to indicate an aggressive course of disease and long-term survival is excellent in about 75% of patients.
- An imageable pancreatic NEN > 2 cm, although most likely non-functioning, seems to be a good surrogate parameter to indicate surgery in order to prevent distant metastatic DP-NEN disease. However, the higher chance of cure when performing a PPD resection at the time of biochemical ZES evidence, even without positive imaging, should be discussed with the patient with regard to benefits and risks. There is no consensus regarding the type of operation for MEN1-ZES.
- It is consensus that any operation for MEN1-ZES should include an exploration of the duodenum via duodenotomy or even resection of the duodenum combined with systematic lymphadenectomy to provide a chance of cure and to reduce the risk of distant metastatic ZES disease.
- The surgical procedure should be individualized according to preoperative findings, the patient's history (e.g., age, pre-existing insulin-dependent diabetes), and the patient's preference.
- Duodenopancreatic resections for MEN1-ZES should only be performed by experienced pancreatic (endocrine) surgeons.

Research agenda

- Parameters or genetic makers indicating an aggressive course of disease are warranted to guide treatment
- Further studies are needed to correlate postoperative biochemical cure and long-term survival.
- Controlled trials comparing more and less extensive resections are needed to determine their effect on long term survival, morbidity, and quality of life.

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